Available online at www.sciencedirect.com

SCIENCE DIRECT®

ELSEVIER

European Journal of Medicinal Chemistry 40 (2005) 1222–1245

EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY

www.elsevier.com/locate/ejmech

Original article

Synthesis and biological evaluation as AChE inhibitors of new indanones and thiaindanones related to donepezil

Ziad Omran, Thomas Cailly, Elodie Lescot, Jana Sopkova-de Oliveira Santos, Jean-Hugues Agondanou, Vincent Lisowski, Frédéric Fabis, Anne-Marie Godard, Silvia Stiebing, Guillaume Le Flem, Michel Boulouard, François Dauphin, Patrick Dallemagne *, Sylvain Rault

Centre d'études et de recherche sur le médicament de Normandie, département de pharmacochimie U.F.R. des sciences pharmaceutiques, université de Caen Basse-Normandie, boulevard Becquerel, 14032 Caen cedex, France

Received 28 April 2005; received in revised form 17 June 2005; accepted 1 July 2005

Available online 30 August 2005

Abstract

Sixty-four new indanones and thiaindanones related to donepezil were synthesized and evaluated in vitro as potential AChE inhibitors. Among them, 11 derivatives were found to inhibit the enzyme in the submicromolar range; the best compound revealed its inhibitory activity with an IC_{50} in the same range (0.06 µM) than the reference compound, donepezil (IC_{50} = 0.02 µM).

Keywords: Alzheimer disease; Donepezil; Acetylcholinesterase; Cyclopentathiophene; Indanone; Thiaindanone

1. Introduction

Alzheimer disease (AD) is characterized by reduced cortical and hippocampal levels of acetylcholine (ACh). Agents that restore the latter through the inhibition of acetylcholinesterase (AChE) constitute as of today the main palliative treatment of this affection [1]. Among AChE inhibitors, donepezil (E2020; **1**) [2], a dimethoxyindanone derivative, exhibits a long and selective action and manageable adverse effects that confer to it a lead position in this pharmacological series in view to design analogues with potential interest in the treatment of AD [3]. Taking our experience in the indanone field into account, we focused on the synthesis and the in vitro biological evaluation as AChE inhibitors of new derivatives **2–65** related to donepezil, prepared from 5,6-dimethoxy-3-aminoindan-1-one **66** and its thiophene isosters **67–75** (Fig. 1) [4–9].

2. Chemistry

The access to the aminocyclopentanone system fused on a benzene or a thiophene ring was achieved as previously described by our group from various benzene or thiophene carboxaldehydes **76–79** (Scheme 1). The synthetic pathway involved the β-aminoacids **80–83** obtained from the latter according to the Rodionow–Johnson [10,11] reaction which were then, eventually after halogenation, cyclized and finally

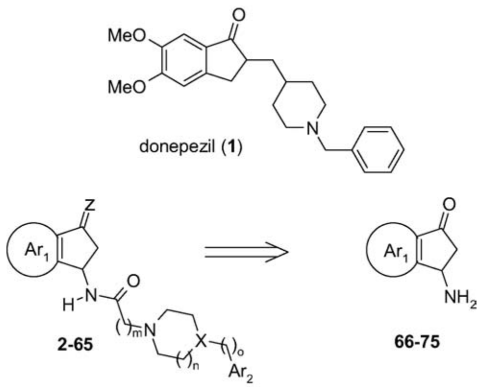
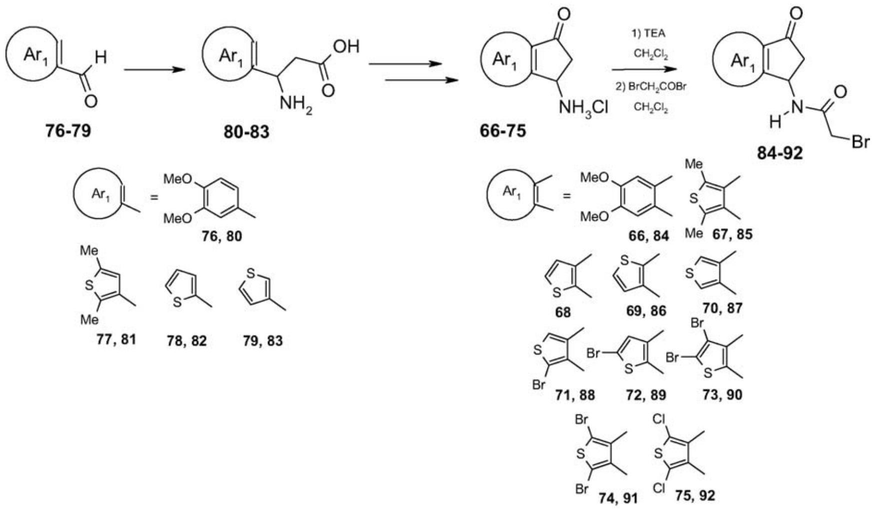


Fig. 1.

* Corresponding author. Tel.: +33 2 31 56 59 10; fax: +33 2 31 93 34 73.
E-mail address: patrick.dallemagne@unicaen.fr (P. Dallemagne).

0223-5234/$ - see front matter
doi:10.1016/j.ejmech.2005.07.009



Scheme 1.

hydrolyzed to yield the hydrochloric salts of the aminocyclopentanones **66–75**. The latter were treated in alkaline medium to liberate the free bases which were then involved in a reaction with bromoacetyl bromide yielding the bromoacetamides **84–92**, which were finally reacted with various N-substituted piperazines to provide the title derivatives **2–58** (Scheme 2).

The commercially unavailable piperazinyl reagents involved in this nucleophilic substitution were prepared from substituted arylmethylhalides by reaction with an excess of piperazine. The unknown N-(pyrrol-2-ylmethyl)- **99** and [(2,5-dimethoxythien-3-yl)]methyl- **100** piperazines were issued from the reductive amination of arylcarboxaldehydes **95**, **96** by ethyl piperazine-carboxylate in the presence of sodium cyanoborohydride and subsequent N-deprotection of the carboxylates **97**, **98** in alkaline medium under microwave application (Scheme 3).

The dibromocyclopenta[c]thiophene series, selected by the biological evaluation, was particularly submitted to various pharmacomodulations. For example, the oximes **59–61** were selectively prepared under their E form starting from **13**, **20** or **43**, respectively, using hydroxylamine displaced from its hydrochloride (Scheme 4).

On the other hand, in a similar manner as above and starting from the corresponding bromoacetamide **91**, the benzylhomopiperazinyl **62** and piperidinyl derivatives **63** were prepared (Scheme 5).

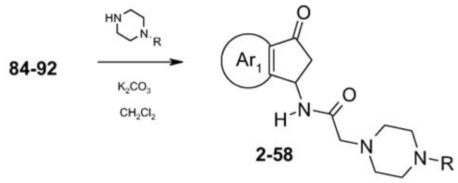
Finally, the length of the linker chain between the piperazinyl and the thiaindanone moieties was declined through the synthesis of the compounds **64** and **65** (Scheme 6). The latter were prepared from the aminodibromocyclopenta[c]thiophene derivative **74** whose the hydrochloric salt was reacted with bromobutyryl- and bromopropionyl chloride, respectively, to give the bromide **93** and the α,β-unsaturated derivative **94**. The latter was issued from a β-elimination which took place in the presence of an excess of TEA, while no traces of the corresponding halide were observed in this case. Compounds **93** and **94** yielded **64** and **65**, respectively, under treatment with 2-chlorobenzylpiperazine.

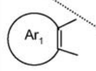
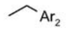
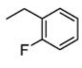
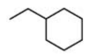
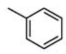
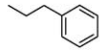
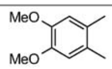
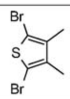
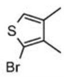
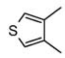
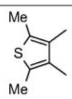
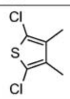
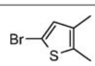
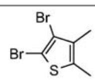
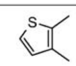
3. Discussion

Compounds **2–65** were tested for in vitro inhibition of AChE on the commercially available electric eel enzyme according to the Ellman et al.'s [12] method. Taking into account the SAR recently established by the structure elucidation of AChE-donepezil co-crystal [13], we first evaluated a dimethoxyindanone derivative **2** substituted on the 3-position by a benzyl-piperazinylacetamide moiety likely to reproduced the interactions between donepezil and AChE. The result (Table 1), however, was quite disappointing since **2** inhibited AChE at a two hundred-fold higher concentration than donepezil (IC_{50} = 4.00 µM versus 0.02 µM).

Substitution of the phenyl ring of **2** by various halogen atoms or groups did not permit to recover the inhibitory activity at the noteworthy exception of the 2-chlorophenyl derivative **9** (IC_{50} = 0.65 µM). On the other hand, replacement of the indanone moiety of **2** by an oxodibromocyclopenta[c]thiophene one slightly improved the activity of compound **12** (IC_{50} = 0.56 µM) and consequently the latter was considered as a new lead for further pharmacomodulations.

So, replacement of the piperazine ring of **12** by piperidine (**63**) or homopiperazine (**62**) resulted in a total loss of anti-AChE activity in a similar manner as for the introduction of a cyclohexylmethyl (**56**), a phenyl (**57**) or a phenethyl (**58**) group in place of the benzyl one (Table 2). Substitution of the latter was also examined. The results showed that introduction of a substituent in the 4- or 3-position resulted in a loss of activity whatever its nature, except for a fluorine atom which however decreased it (**22**, IC_{50} = 1.40 µM and **21**, IC_{50} = 2.50 µM). In the mean time and in a similar manner than for the indanone series, substitution of the 2-position of the benzyl group by a chlorine (**13**, IC_{50} = 0.22 µM), fluorine (**20**, IC_{50} = 0.40 µM) or bromine atom (**23**, IC_{50} = 0.58 µM) or a methyl group (**26**, IC_{50} = 0.75 µM) preserved or improved the anti-AChE activity at the condition that the other phenyl positions remain unsubstituted. It was not the case for the derivatives bearing on this 2-position an iodine atom (**24**), a

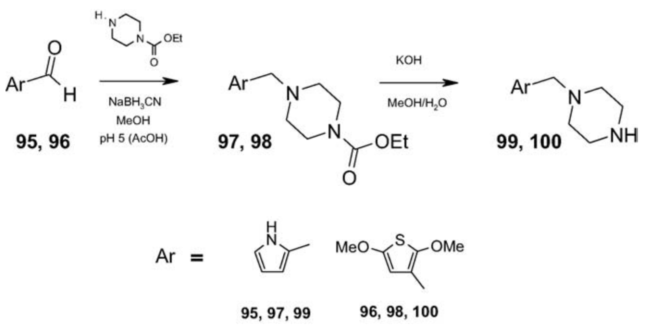


 R					
	**2-12** (Ar_2 : see Table 1)	-	-	-	-
	**13-19; 21-48** (Ar_2 : see Table 2)	**20**	**56**	**57**	**58**
	-	**49**	-	-	-
	-	**50**	-	-	-
	-	**51**	-	-	-
	-	**52**	-	-	-
	-	**53**	-	-	-
	-	**54**	-	-	-
	-	**55**	-	-	-

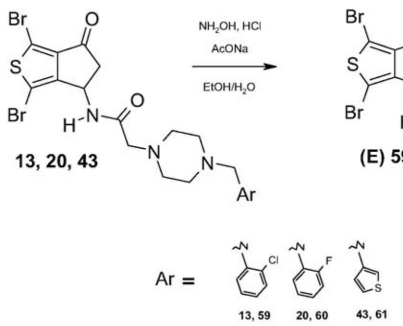
Scheme 2.

trifluoromethyl (**25**), a nitro (**29**), an amino (**32**), or a methoxy group (**34**) which were almost devoid of activity. In a similar manner, replacement of the phenyl ring of the benzyl moiety by a naphthalene (**38**), a pyridine (**39–41**), a furane (**46**, **47**) or a pyrrole (**48**) ring dramatically resulted in decreased activity. The latter was nevertheless preserved at a lower level with a 2-thiophene ring (**42**, IC_{50} = 1.25 µM) and even increased with a 3-thiophene one (**43**, IC_{50} = 0.18 µM). Substitution of the thiophene ring of **42** and **43** by a chlorine atom (**44**) or by two methoxy groups (**45**), respectively, however suppressed the activity.

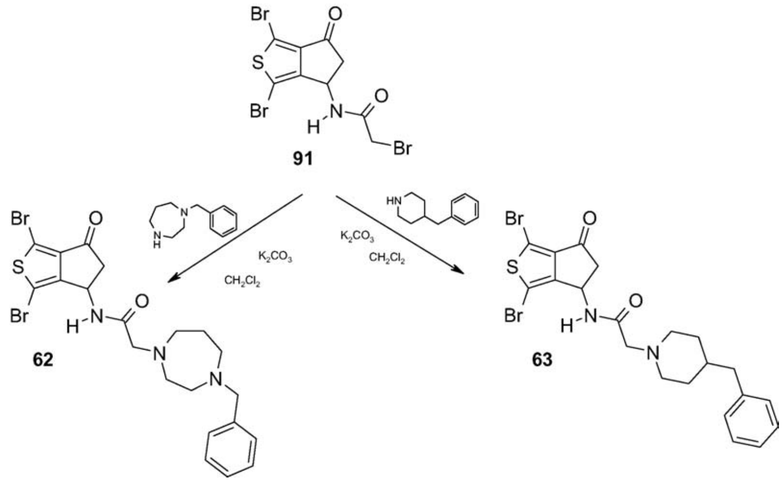
On the other hand, compounds **64** and **65**, the upper homologues of **13**, showed that the acetamido group between the cyclopentane moiety and the piperazine one is critical for anti-AChE activity since these compounds were almost devoid of activity (Table 3).



Scheme 3.



Scheme 4.



Scheme 5.

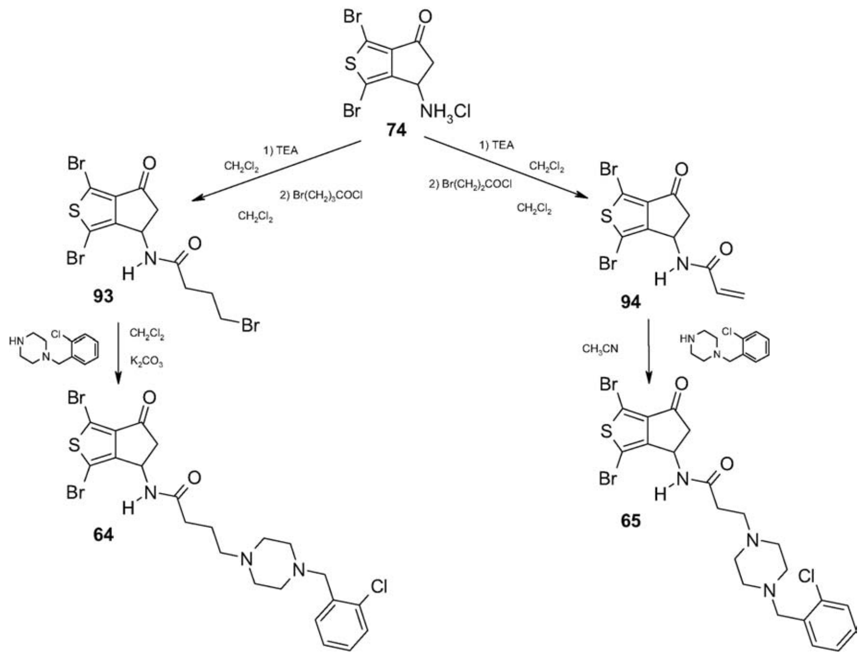
The effect of the position of the sulfur atom of the thiophene ring as well as the nature of the substituents of the latter on the activity of **20** were then examined (Table 4). It appeared that the cyclopentane ring must be fused on the c-side of the thiophene since the cyclopenta[b] thiophene derivatives **53–55** were inactive. The thiophene ring must be further substituted on the 1- and 3-positions by two methyl groups (**51**, IC_{50} = 0.57 μM), or halogen atoms since the dibromo compound **20** remained three to four-fold more active than its 1-monobromo derivative (**49**, IC_{50} = 1.10 μM) or than its dichloro analog (**52**, IC_{50} = 1.50 μM) and the unsubstituted derivative **50** totally losing the activity.

Finally, the role of the cyclopentane carbonyl of the most active compounds **13**, **20** and **43** was studied through its condensation into an oxime group (Table 5). Compound **59** was totally devoid of the activity of **13**, whereas **61** (IC_{50} = 0.14 μM) conserved those of **43**. In the 2-fluorobenzyl series, the oxime (**60**, IC_{50} = 0.06 μM) significantly improved the inhibitory activity of the oxo derivative **20**.

4. Molecular modeling

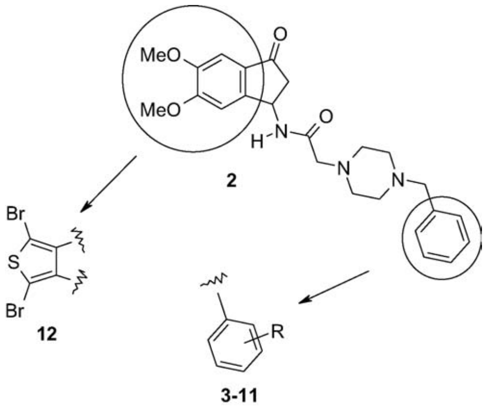
The crystal structure of AChE cocrystallized with donepezil **1** [13], showed that donepezil binds in the active-site cleft principally by (i) stacking interaction of indanone with Trp_{279} and (ii) stacking interaction of the benzyl ring with Trp_{84} (Fig. 2). (iii) A π-cation interaction occurs between the charged nitrogen of the piperidine ring and the phenyl ring of Phe_{330}. No direct hydrogen bond between the enzyme and donepezil could be detected in the structure; donepezil binds to the enzyme via hydrogen bonds through water molecules (iv).

A 3D model of the inhibitor molecules was built and positioned into the AChE cleft automatically by the program



Scheme 6.

Table 1
Anti-AchE activity of compounds **1–12**



Compd[a]	R	IC_{50} ± SD (μM)[b]
1	–	0.02 ± 0.01 (*N* = 4)[c]
2	–	4.00 (*N* = 1)
3	4-OMe	Inactive
4	4-Br	Inactive
5	4-Cl	Inactive
6	3-CF_3	Inactive
7	3-Cl	Inactive
8	3-CN	Inactive
9	2-Cl	0.65 ± 0.05 (*N* = 2)
10	2-NO_2	Inactive
11	2,6-diCl	Inactive
12	–	0.56 ± 0.05 (*N* = 2)

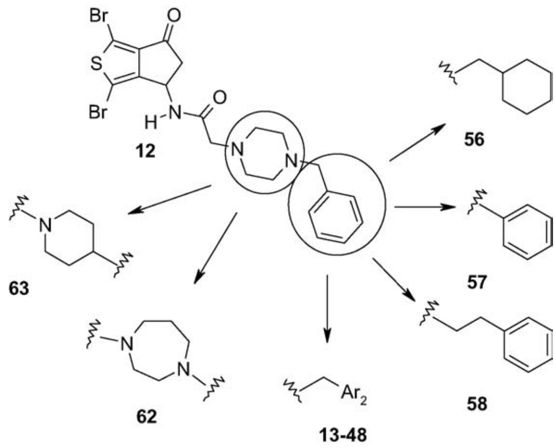
[a] The value of the hydrochloride is shown.
[b] IC_{50} value was measured for enzyme activity < 20% at 10^{-5} M.
[c] *N* = number of duplicate independent experiments.

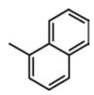
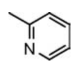
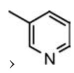
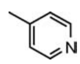
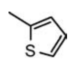
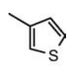
LigandFit (Cerius2) [14]. The position of **12** we found is very similar to that of donepezil (Fig. 2). In the bottom part, the interactions of donepezil are conserved: (i) the benzyl moiety stacks against the indole ring of Trp_{84} and (ii) the charged nitrogen of the piperazine ring is oriented in a position suitable for a π-cation interaction with the phenyl ring Phe_{330}. The differences are observed in upper part, the dibromocyclopenta [c]thiophene moiety takes different orientations with respect to Trp_{279}. (iii) The π-stacking interaction between this moiety and the indole is perturbed, and the bromine atom at position 1 on the thiophene is oriented outside of the protein cavity contrary to the brome at position 3, which is oriented inside of the protein, in a hydrophobic environment.

In vitro tests showed that substitution of the ortho position of the benzyl ring by a chlorine (compound **13**) or fluorine atom (compound **20**) increases the inhibitory activity. Modeling studies on **20** showed that substitution of the benzyl at the ortho position by a fluorine atom modifies the orientation of the benzyl ring in a manner that its π-stacking with the Trp_{84} is amplified.

We further observed that the presence of a hydrophobic aromatic group on the place of a benzyl group is favorable for a good affinity. The best inhibition activity was observed for the thiophene derivative **43**. Sulfur is a hydrophobic atom and its presence in the ring enhanced the hydrogen bond donor capacity of two neighboring carbons (Fig. 3). Along to our

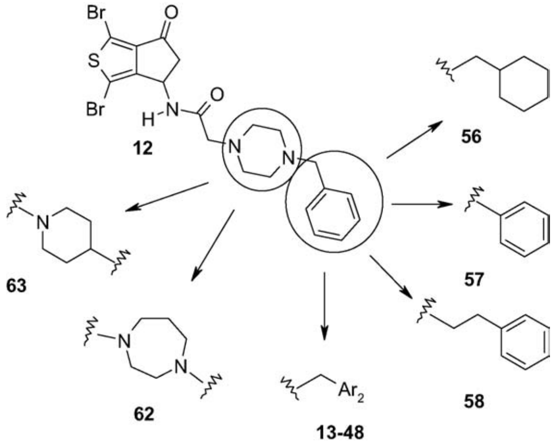
Table 2
Anti-AchE activity of compounds **12–48**, **56–58**, **62**, **63**

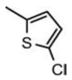
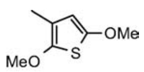
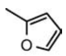
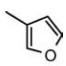
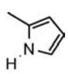


Compd	Ar_2	IC_{50} ± SD (μM)[b]
12[a]	–	0.56 ± 0.05 (*N* = 2)[c]
13[a]	2-Cl-C_6H_4	0.22 ± 0.01 (*N* = 2)
14	3-Cl-C_6H_4	Inactive
15	4-Cl-C_6H_4	Inactive
16	2,3-diCl-C_6H_3	Inactive
17[a]	2,4-diCl-C_6H_3	Inactive
18[a]	2,5-diCl-C_6H_3	Inactive
19	2,6-diCl-C_6H_3	Inactive
20[a]	2-F-C_6H_4	0.40 ± 0.07 (*N* = 3)
21[a]	3-F-C_6H_4	2.50 ± 0.20 (*N* = 2)
22[a]	4-F-C_6H_4	1.40 ± 0.20 (*N* = 2)
23[a]	2-Br-C_6H_4	0.58 ± 0.03 (*N* = 2)
24	2-I-C_6H_4	Inactive
25[a]	2-CF_3-C_6H_4	Inactive
26[a]	2-Me-C_6H_4	0.75 ± 0.65 (*N* = 3)
27[a]	3-Me-C_6H_4	Inactive
28[a]	4-Me-C_6H_4	Inactive
29	2-NO_2-C_6H_4	Inactive
30[a]	3-NO_2-C_6H_4	Inactive
31[a]	4-NO_2-C_6H_4	Inactive
32[a]	2-NH_2-C_6H_4	1.40 ± 0.60 (*N* = 3)
33[a]	4-NH_2-C_6H_4	Inactive
34[a]	2-OMe-C_6H_4	Inactive
35	3-OMe-C_6H_4	Inactive
36[a]	4-OMe-C_6H_4	Inactive
37[a]	3,4-diOMe-C_6H_3	Inactive
38		Inactive
39[a]		Inactive
40[a]		Inactive
41[a]		Inactive
42[a]		1.25 ± 0.25 (*N* = 2)
43[a]		0.18 ± 0.01 (*N* = 2)

(continued on next page)

Table 2
(continued)



Compd	Ar_2	IC_{50} ± SD (µM)[b]
44[a]		Inactive
45[a]		Inactive
46[a]		Inactive
47[a]		Inactive
48[a]		Inactive
56	–	Inactive
57[a]	–	Inactive
58	–	Inactive
62[a]	–	Inactive
63	–	Inactive

[a] The value of the hydrochloride is shown.
[b] IC_{50} value was measured for enzyme activity < 20% at 10^{-5} M.
[c] *N* = number of duplicate independent experiments.

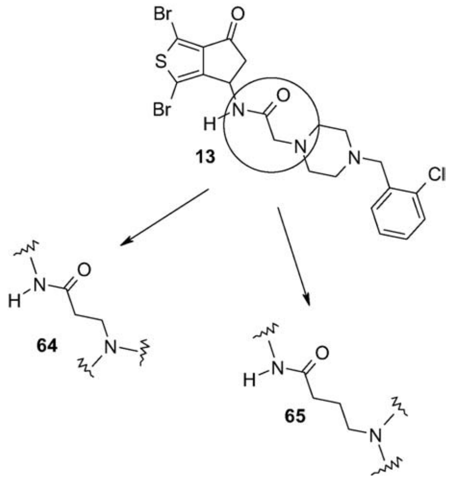
docking results the thiophene ring is situated in the way that one of the neighboring carbons is opposite to the carbonyl of glutamic acid at a distance favorable for the formation of a weak hydrogen bond ($d_{C–H}$~3.5Å). Therefore, the thiophene interacts through π–π stacking and in the same time through weak hydrogen bond with AChE.

In vitro tests revealed furthermore that the oxime **60** corresponding to the orthofluorobenzyl derivative **20** exerts an inhibitory activity on AChE close to the donepezil one. Modeling studies showed that the upper part is differently positioned differently between **60** and **20**. For the latter, it takes a position in which π–π stacking with the indole ring of Trp_{279} is better preserved and in which the oxime group makes a hydrogen bond with the carboxyl group of Ser_{286} (Fig. 4).

5. Conclusion

We have synthesized and evaluated as potential AChE inhibitors 64 new indanones and thiaindanones related to

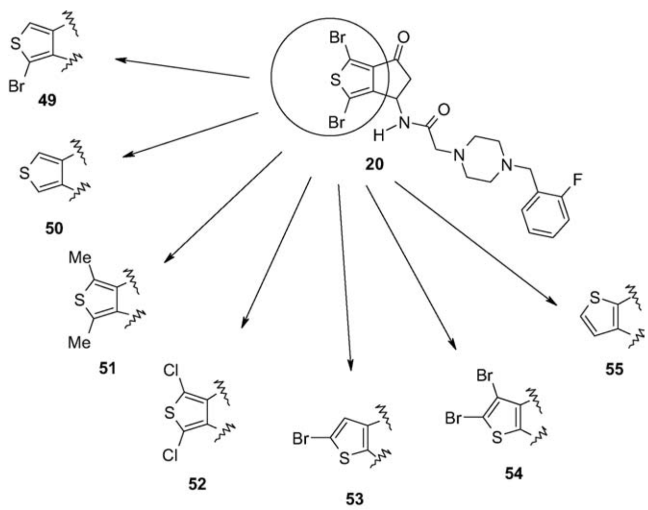
Table 3
Anti-AchE activity of compounds **13**, **64**, **65**



Compd[a]	IC_{50} ± SD (µM)[b]
13	0.22 ± 0.01 (*N* = 2)[c]
64	Inactive
65	Inactive

[a] The value of the hydrochloride is shown.
[b] IC_{50} value was measured for enzyme activity < 20% at 10^{-5} M.
[c] *N* = number of duplicate independent experiments.

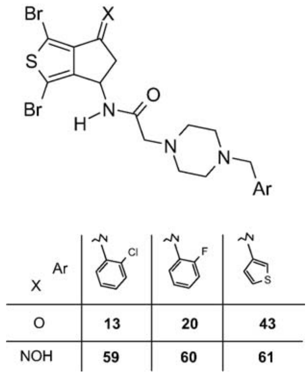
Table 4
Anti-AchE activity of compounds **20**, **49–55**



Compd[a]	IC_{50} ± S.D. (µM)[b]
20	0.40 ± 0.07 (*N* = 3)[c]
49	1.10 ± 0.20 (*N* = 2)
50	Inactive
51	0.57 ± 0.13 (*N* = 2)
52	1.50 ± 0.30 (*N* = 2)
53	Inactive
54	Inactive
55	Inactive

[a] The value of the hydrochloride is shown.
[b] IC_{50} value was measured for enzyme activity < 20% at 10^{-5} M.
[c] *N* = number of duplicate independent experiments.

Table 5
Anti-AchE activity of compounds **13**, **20**, **43**, **59–61**



Compd	IC_{50} ± S.D. (μM)[b]
13[a]	0.22 ± 0.01 (*N* = 2)[c]
20[a]	0.40 ± 0.07 (*N* = 3)
43[a]	0.18 ± 0.01 (*N* = 2)
59	Inactive
60	0.06 ± 0.02 (*N* = 3)
61	0.14 ± 0.07 (*N* = 2)

[a] The value of the hydrochloride is shown.
[b] IC_{50} value was measured for enzyme activity < 20% at 10^{-5} M.
[c] *N* = number of independent experiments.

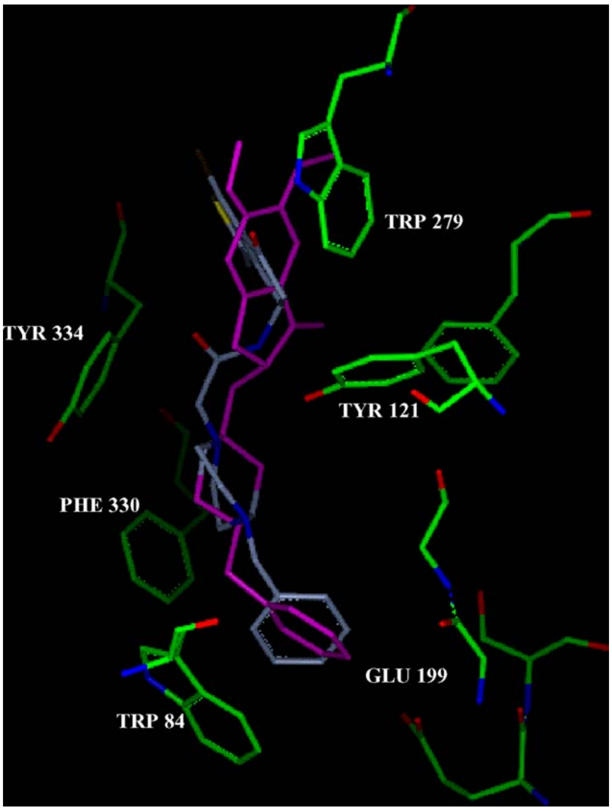


Fig. 2. The stick representation of the binding site of AChE (green) and donepezil (gray) from X-ray structure, with the modeled position of compound **12** (purple).

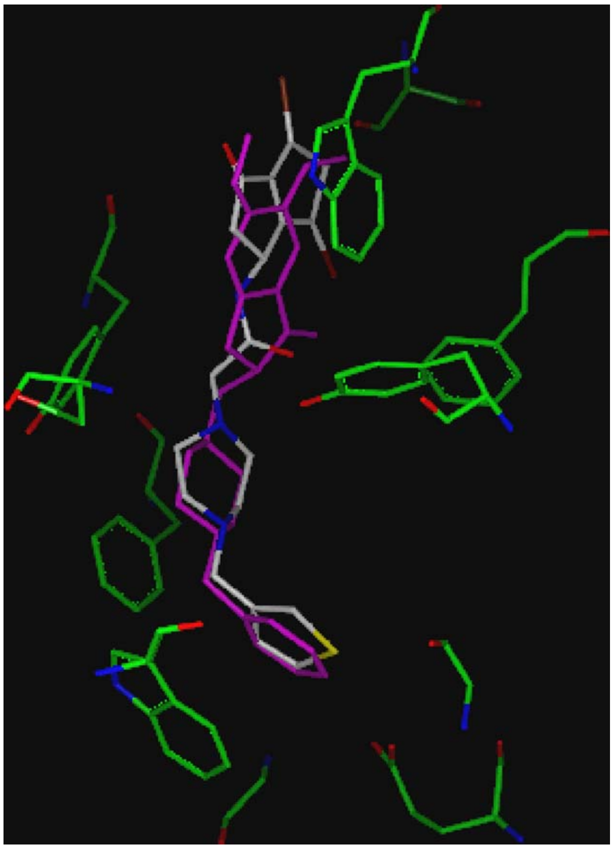


Fig. 3. The stick representation of the binding site of AChE (green) and donepezil (purple) from X-ray structure, with the modeled position of compound **43** (gray).

donepezil. Among them, 11 derivatives were found to inhibit the enzyme in the submicromolar range and one of them (**60**), revealed its inhibitory activity with an IC_{50} (0.06 μM) in a same order of magnitude than the reference compound, donepezil (**1**, IC_{50} = 0.02 μM). This result prompts us to now study the in vivo biological comportment of these new inhibitors.

6. Experimental protocols

6.1. In vitro tests of AChE biological activity

Inhibitory capacity of compounds on AChE biological activity were evaluated through the use of the spectrometric method of Ellman et al. [12]. Lyophilized electric eel AChE (Type III, electric eel, Sigma Chemical Co.) was dissolved in 0.2 M phosphate buffer pH 7.4 such as to have an enzyme solution stock with 2.5 units.ml^{-1} AChE activity. Acetylthiocholine iodide (Sigma Chemical Co.) was used as a substrate of the enzymatic reaction and 5,5-dithiobis-(2-nitrobenzoic) acid (DTNB, Sigma Chemical Co.) as label for the measurement of cholinesterase activity. In the procedure, 1880 μL of 60 mg/500 ml DTNB dissolved in phosphate buffer pH 7.4 were mixed with 40 μl of test compound solution and 40 μl of enzyme stock solution were mixed. After 5 min of preincubation, 40 μl of 10 mM acetylthio-choline iodide solu-

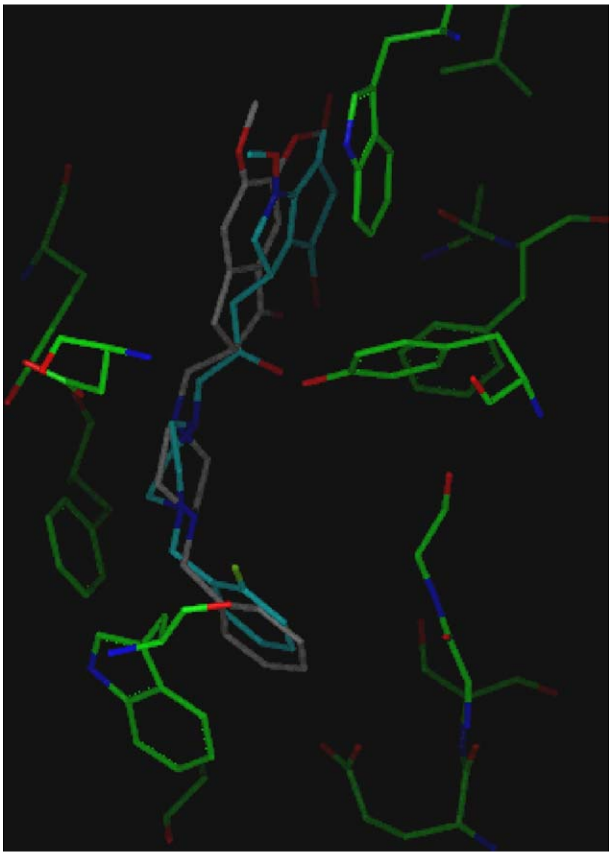


Fig. 4. The stick representation of the binding site of AChE (green) and donepezil (gray) from X-ray structure, with the modeled position of compound **60** (cyan).

tion was added to the assay solution. The change in absorbance at 412 nm was recorded (AGILENT 8453 UV–VIS Spectroscopy System) during 10 min First screening of AChE activity was carried out at a 10^{-5} M concentration of compounds under study. For the compounds with significant inhibition (≥ 80%) after 4 min of reaction, IC_{50} values were determined graphically from log concentration–inhibition curves, using a range of 10^{-10}–10^{-3} M concentrations of the test compounds.

6.2. Computational methods

6.2.1. Inhibitor structures

The 3D models of inhibitors were generated using the Cerius2 software (Accelerys Co.). To derive a stable conformation for the models, the full geometry optimization was carried out by semiempirical AM1 method (MOPAC program in Cerius2 software [15–17]).

6.2.2. Complex models

The crystal structure of complex AChE from Torpedo Californica/Donepezil (E2020) (PDB file identificator 1EVE) [13] was used as template to construct the complex models. The studied compounds were placed automatically by docking procedure of LigandFit [14] in the active-site cleft of protein model.

6.3. Chemistry

Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were recorded on a Genesis series FTIR spectrometer using KBr pellets. The ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were obtained on a Jeol Lambda 400 spectrometer using DMSO-d_6 or $CDCl_3$. The chemical shifts (δ) are reported in ppm, and the coupling constants are in Hertz. Electron impact mass spectra were obtained using a Jeol JMS GCMate spectrometer and with pfk as internal standard for high-resolution procedure. Reactions were monitored by thin-layer chromatography (TLC) using 0.2 mm Polygram Sil silica gel G/UV 254 precoated plates with visualization by irradiation with a short-wavelength UV light. Silica gel flash chromatography was performed using 63–200 mM Kieselgel Merck 60 silica gel.

*6.4. General experimental procedure for the synthesis of **2–58**, **62–64***

To a solution of one of the compounds **84–93** (1.5 mmol) in methylene chloride (10 ml) was added the desired piperazine, piperidine or homopiperazine derivative (3 mmol) and potassium carbonate (0.426 g, 3 mmol). The reaction mixture was stirred at room temperature for 12 h. Methylene chloride (50 ml) was then added and the mixture was washed several times with water. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The product was purified by flash chromatography.

*6.4.1. 2-(4-Benzylpiperazin-1-yl)-N-(5,6-dimethoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)acetamide (**2**)*

Yield: 89%. M.P. 190 °C. IR (KBr, cm^{-1}): 3309 (NH), 1690 (CO), 1659 (CO amide), 1503, 1452, 1302, 1213, 840, 735. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.28 (m, 5H, H_{phenyl}), 7.18 (s, 1H, H-4), 6.95 (s, 1H, H-7), 6.77 (d, $^{3}J_{NH\text{-}H1c}$ = 9.0 Hz, 1H,NH), 5.65 (m, 1H, H-3), 3.93 (s, 6H, 2OMe), 3.47 (s, 2H, H_{benzyl}), 3.20 (dd, $^{3}J_{H2b\text{-}H1c}$ = 7.5 Hz, $^{2}J_{H2b\text{-}H2a}$ = 18.9 Hz, 1H, H-2b), 3.09 (s, 2H, COCH_2N), 2.42(m, 9H, H-2a and $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 201.75 (C-3), 170.50 (NHCO), 156.06 (C-6), 150.82 (C-5), 149.30 (C-7a), 137.78 (C-1_{phenyl}), 129.72 (C-3a), 129.10 (C-2_{phenyl} and C-6_{phenyl}), 128.28 (C-3_{phenyl} and C-5_{phenyl}), 127.19 (C-4_{phenyl}), 106.53 (C-7), 103.57 (C-4), 64.43 (COCH_2N), 62.17 (C_{benzyl}), 56.57 (OMe), 56.24 (OMe), 53.58 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.90 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 46.45 (C-1), 44.92 (C-2). HRMS: calculated (423.2158), found (423.2222).

*6.4.2. 2-[4-(4-Methoxybenzyl)piperazin-1-yl]-N-(5,6-dimethoxy-3-oxo-2,3-dihydro-1H-inden-1-yl) acetamide (**3**)*

Yield: 15%. M.P. 195 °C. IR (KBr, cm^{-1}): 3310 (NH), 1705 (CO), 1660 (CO amide), 1594, 1461, 1332, 1051, 1010, 841. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.40 (d, $^{3}J_{NH\text{-}H1c}$ = 9.3 Hz, 1H,NH), 7.00 (m, 6H, H-4, H-7 and H_{phenyl}), 5.65 (m, 1H, H-3), 3.93 (s, 6H, 2OMe), 3.79 (s, 3H, OMe), 3.45 (s, 2H,

H_{benzyl}), 3.20 (dd, $^3J_{H2b\text{-}H1c}$ = 7.5 Hz, $^2J_{H2b\text{-}H2a}$ = 18.8 Hz, 1H, H-2b), 3.08 (s, 2H, COC*H*$_2$N), 2.48 (m, 9H, H-2a and $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 201.76 (C-3), 170.22 (NHCO), 160.00 (C-4$_{phenyl}$), 155.84 (C-6), 150.60 (C-5), 149.88 (C-7a), 129.49 (C-3a), 129.04 (C-1$_{phenyl}$), 121.21 (C-2$_{phenyl}$ and C-6$_{phenyl}$), 114.45 (C-3$_{phenyl}$ and C-5$_{phenyl}$), 106.31 (C-7), 103.53 (C-4), 62.45 (C_{benzyl}), 61.16 (CO*C*H$_2$N), 56.24 (OMe), 56.00 (OMe), 54.98 (OMe), 53.22 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.61 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 46.23 (C-1), 44.68 (C-2). MS (m/z): 453.2 ($^+$M).

*6.4.3. 2-[4-(4-Bromobenzyl)piperazin-1-yl]-N-(5,6-dimethoxy-3-oxo-2,3-dihydro-1H-inden-1-yl) acetamide (**4**)*

Yield: 95%. M.P. 222 °C. IR (KBr, cm^{-1}): 3338 (NH), 1706 (CO), 1640 (CO amide), 1593, 1505, 1462, 1309, 1266, 845. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.10 (m, 6H,NH, H-4 and H_{phenyl}), 6.95 (s, 1H, H-7), 5.66 (m, 1H, H-3), 3.93 (s, 6H, 2OMe), 3.41 (s, 2H, H_{benzyl}), 3.20 (dd, $^3J_{H2b\text{-}H1c}$ = 7.6 Hz, $^2J_{H2b\text{-}H2a}$ = 18.8 Hz, 1H, H-2b), 3.09 (s, 2H, COC*H*$_2$N), 2.48 (m, 9H, H-2a and $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 201.68 (C-3), 170.37 (NHCO), 156.03 (C-6), 150.81 (C-5), 149.25 (C-7a), 136.86 (C-1$_{phenyl}$), 131.35 (C-3$_{phenyl}$ and C-5$_{phenyl}$), 130.63 (C-2$_{phenyl}$ and C-6$_{phenyl}$), 129.69 (C-3a), 120.95 (C-4$_{phenyl}$), 106.52 (C-7), 103.73 (C-4), 62.01 (C_{benzyl}), 61.36 (CO*C*H$_2$N), 56.42 (OMe), 56.20 (OMe), 53.48 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.82 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 46.40 (C-1), 44.87 (C-2). HRMS: calculated (501.1263), found (501.1246).

*6.4.4. 2-[4-(4-Chlorobenzyl)piperazin-1-yl]-N-(5,6-dimethoxy-3-oxo-2,3-dihydro-1H-inden-1-yl) acetamide (**5**)*

Yield: 12%. M.P. 218 °C. IR (KBr, cm^{-1}): 3447 (NH), 1689 (CO), 1660 (CO amide), 1595, 1505, 1456, 1330, 1267, 986. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.42 (d, $^3J_{NH\text{-}H1c}$ = 8.7 Hz, 1H,NH), 7.20 (m, 5H, H-4 and H_{phenyl}), 6.95 (s, 1H, H-7), 5.66 (m, 1H, H-3), 3.93 (s, 6H, 2OMe), 3.43 (s, 2H, H_{benzyl}), 3.20 (dd, $^3J_{H2b\text{-}H1c}$ = 7.5 Hz, $^2J_{H2b\text{-}H2a}$ = 18.8 Hz, 1H, H-2b), 3.09 (s, 2H, COC*H*$_2$N), 2.48 (m, 9H, H-2a and $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 201.03 (C-3), 170.44 (NHCO), 156.05 (C-6), 150.81 (C-5), 149.29 (C-7a), 136.34 (C-1$_{phenyl}$), 132.89 (C-4$_{phenyl}$), 130.31 (C-2$_{phenyl}$ and C-6$_{phenyl}$), 129.70 (C-3a), 128.44 (C-3$_{phenyl}$ and C-5$_{phenyl}$), 106.53 (C-7), 103.71 (C-4), 62.00 (CO*C*H$_2$N), 61.28 (C_{benzyl}), 56.47 (OMe), 56.24 (OMe), 53.51 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.48 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 46.41 (C-1), 44.89 (C-2). HRMS: calculated (457.1768), found (457.1719).

*6.4.5. 2-[4-(3-Trifluoromethylbenzyl)piperazin-1-yl]-N-(5,6-dimethoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)acetamide (**6**)*

Yield: 16%. M.P. 130 °C. IR (KBr, cm^{-1}): 3446 (NH), 1689 (CO), 1660 (CO amide), 1595, 1505, 1456, 1330, 1121, 986. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.50 (m, 5H,NH and H_{phenyl}), 7.18 (s, 1H, H-4), 6.95 (s, 1H, H-7), 5.66 (m, 1H, H-3), 3.93 (s, 6H, 2OMe), 3.51 (s, 2H, H_{benzyl}), 3.20 (dd, $^3J_{H2b\text{-}H1c}$ = 7.4 Hz, $^2J_{H2b\text{-}H2a}$ = 18.9 Hz, 1H, H-2b), 3.10 (s, 2H, COC*H*$_2$N), 2.48 (m, 9H, H-2a and $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 201.78 (C-3), 170.35 (NHCO), 156.05 (C-6), 150.81 (C-5), 149.28 (C-7a), 139.00 (C-1$_{phenyl}$), 132.25 (C-6$_{phenyl}$), 130.67 (q, $^2J_{C\text{–}F}$ = 131.4 Hz, CF_3), 129.75 (C-3a), 129.72 (C-3$_{phenyl}$), 128.76 (C-5$_{phenyl}$), 125.55 (C-4$_{phenyl}$), 124.12 (C-2$_{phenyl}$), 106.31 (C-7), 103.53 (C-4), 62.45 (C_{benzyl}), 61.16 (CO*C*H$_2$N), 56.47 (OMe), 56.24 (OMe), 53.46 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.90 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 46.43 (C-1), 44.89 (C-2). HRMS: calculated (491.2032), found (491.1996).

*6.4.6. 2-[4-(3-Chlorobenzyl)piperazin-1-yl]-N-(5,6-dimethoxy-3-oxo-2,3-dihydro-1H-inden-1-yl) acetamide (**7**)*

Yield: 46%. M.P. 145 °C. IR (KBr, cm^{-1}): 3348 (NH), 1705 (CO), 1650 (CO amide), 1594, 1503, 1461, 1303, 1211, 1011. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.42 (d, $^3J_{NH\text{-}H1c}$ = 8.7 Hz, 1H,NH), 7.50 (m, 5H, H-4 and H_{phenyl}), 6.95 (s, 1H, H-7), 5.66 (m, 1H, H-3), 3.93 (s, 6H, 2OMe), 3.43 (s, 2H, H_{benzyl}), 3.21 (dd, $^3J_{H2b\text{-}H1c}$ = 7.4 Hz, $^2J_{H2b\text{-}H2a}$ = 18.9 Hz, 1H, H-2b), 3.09 (s, 2H, COC*H*$_2$N), 2.48 (m, 9H, H-2a and $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 201.75 (C-3), 170.04 (NHCO), 156.07 (C-6), 150.84 (C-5), 149.29 (C-7a), 140.10 (C-3$_{phenyl}$), 134.21 (C-1$_{phenyl}$), 129.74 (C-3a), 129.55 (C-5$_{phenyl}$), 128.95 (C-2$_{phenyl}$), 127.40 (C-6$_{phenyl}$), 127.07 (C-4$_{phenyl}$), 106.54 (C-7), 103.75 (C-4), 62.17 (CO*C*H$_2$N), 61.41 (C_{benzyl}), 56.47 (OMe), 56.24 (OMe), 53.53 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.90 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 46.45 (C-1), 44.92 (C-2). HRMS: calculated (457.1768), found (457.1742).

*6.4.7. 2-[4-(3-Cyanobenzyl)piperazin-1-yl]-N-(5,6-dimethoxy-3-oxo-2,3-dihydro-1H-inden-1-yl) acetamide (**8**)*

Yield: 88%. M.P. 118 °C. IR (KBr, cm^{-1}): 3314 (NH), 1679 (CO), 1660 (CO amide), 1594, 1500, 1457, 1303, 1214, 861. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.48 (m, 5H,NH and H_{phenyl}), 7.18 (s, 1H, H-4), 6.97 (s, 1H, H-7), 5.66 (m, 1H, H-3), 3.92 (s, 6H, 2OMe), 3.47 (s, 2H, H_{benzyl}), 3.19 (dd, $^3J_{H2b\text{-}H1c}$ = 8.2 Hz, $^2J_{H2b\text{-}H2a}$ = 20.0 Hz, 1H, H-2b), 3.09 (s, 2H, COC*H*$_2$N), 2.43 (m, 9H, H-2a and $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 201.74 (C-3), 170.36 (NHCO), 156.09 (C-6), 150.86 (C-5), 149.30 (C-7a), 139.78 (C-1$_{phenyl}$), 133.23 (C-6$_{phenyl}$), 132.20 (C-4$_{phenyl}$), 130.95 (C-2$_{phenyl}$), 129.71 (C-3a), 129.13 (C-5$_{phenyl}$), 118.48 (CN), 112.48 (C-3$_{phenyl}$), 106.59 (C-7), 103.76 (C-4), 61.81 (CO*C*H$_2$N), 61.38 (C_{benzyl}), 56.47 (OMe), 56.24 (OMe), 53.47 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.91 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 46.46 (C-1), 44.87 (C-2). HRMS: calculated (448.2111), found (448.2085).

*6.4.8. 2-[4-(2-Chlorobenzyl)piperazin-1-yl]-N-(5,6-dimethoxy-3-oxo-2,3-dihydro-1H-inden-1-yl) acetamide (**9**)*

Yield: 57%. M.P. 160 °C. IR (KBr, cm^{-1}): 3333 (NH), 1698 (CO), 1673 (CO amide), 1595, 1504, 1300, 1212, 1120, 865. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.30 (m, 6H,NH, H-4 and H_{phenyl}), 6.96 (s, 1H, H-7), 5.66 (m, 1H, H-3), 3.93 (s, 6H, 2OMe), 3.47 (s, 2H, H_{benzyl}), 3.21 (dd, $^3J_{H2b\text{-}H1c}$ = 7.4 Hz, $^2J_{H2b\text{-}H2a}$ = 18.9 Hz, 1H, H-2b), 3.18 (s, 2H, COC*H*$_2$N), 2.43

(m, 9H, H-2a and $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 201.72 (C-3), 170.38 (NHCO), 156.06 (C-6), 150.83 (C-5), 149.21 (C-7a), 134.38 (C-1_{phenyl}), 131.60 (C-2_{phenyl}), 130.86 (C-6_{phenyl}), 129.75 (C-3a), 129.52 (C-3_{phenyl}), 128.411 (C-4_{phenyl}), 126.68 (C-5_{phenyl}), 106.50 (C-7), 103.76 (C-4), 61.37 (CO*C*H_2N), 58.89 (C_{benzyl}), 56.47 (OMe), 56.24 (OMe), 53.46 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.81 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 46.50 (C-1), 44.93 (C-2). HRMS: calculated (457.1768), found (457.1749).

*6.4.9. 2-[4-(2-Nitrobenzyl)piperazin-1-yl]-N-(5,6-dimethoxy-3-oxo-2,3-dihydro-1H-inden-1-yl) acetamide (**10**)*

Yield: 70%. M.P. 126 °C. IR (KBr, cm^{-1}): 3311 (NH), 1697 (CO), 1666 (CO amide), 1594, 1500, 1303, 1266, 1123, 861. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.79 (d, $^3J_{NH-H1c}$ = 7.8 Hz, 1H,NH), 7.45 (m, 4H, H_{phenyl}), 7.17 (s, 1H, H-4), 6.94 (s, 1H, H-7), 5.66 (m, 1H, H-3), 3.93 (s, 6H, 2OMe), 3.75 (s, 2H, H_{benzyl}), 3.20 (dd, $^3J_{H2b-H1c}$ = 7.3 Hz, $^2J_{H2b-H2a}$ = 18.9 Hz, 1H, H-2b), 3.07 (s, 2H, CO*C*H_2N), 2.43 (m, 9H, H-2a and $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 201.72 (C-3), 170.33 (NHCO), 156.06 (C-6), 150.82 (C-5), 149.85 (C-2_{phenyl}), 149.21 (C-7a), 133.34 (C-1_{phenyl}), 132.32 (C-5_{phenyl}), 130.91 (C-4_{phenyl}), 129.75 (C-3a), 127.13 (C-6_{phenyl}), 124.44 (C-3_{phenyl}), 106.50 (C-7), 103.74 (C-4), 61.31 (CO*C*H_2N), 58.81 (C_{benzyl}), 56.47 (OMe), 56.24 (OMe), 53.06 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.92 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 46.44 (C-1), 44.91 (C-2). HRMS: calculated (468.2008), found (468.2022).

*6.4.10. 2-[4-(2,6-Dichlorobenzyl)piperazin-1-yl]-N-(5,6-dimethoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)acetamide (**11**)*

Yield: 40%. M.P. 198 °C. IR (KBr, cm^{-1}): 3325 (NH), 1700 (CO), 1641 (CO amide), 1595, 1499, 1303, 1267, 1121, 860. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.46 (d, $^3J_{NH-H1c}$ = 8.5 Hz, 1H,NH), 7.29 (d, $^3J_{H3phenyl-H4phenyl}$ = $^3J_{H5phenyl-H4phenyl}$ = 7.5 Hz, 2H, H-3_{phenyl} and H-5_{phenyl}), 7.19 (s, 1H, H-4), 7.13 (t, $^3J_{H4phenyl-H3phenyl}$ = $^3J_{H4phenyl-H5phenyl}$ = 7.5 Hz, 1H, H-4_{phenyl}), 6.96 (s, 1H, H-7), 5.65 (m, 1H, H-3), 3.95 (s, 3H, OMe), 3.93 (s, 3H, OMe), 3.71 (s, 2H, H_{benzyl}), 3.22 (dd, $^3J_{H2b-H1c}$ = 7.5 Hz, $^2J_{H2b-H2a}$ = 18.8 Hz, 1H, H-2b), 3.06 (s, 2H, CO*C*H_2N), 2.43 (m, 9H, H-2a and $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 201.77 (C-3), 170.58 (NHCO), 156.09 (C-6), 150.86 (C-5), 149.26 (C-7a), 136.94 (C-2_{phenyl} and C-6_{phenyl}), 134.00 (C-1_{phenyl}), 129.79 (C-3a), 128.94 (C-4_{phenyl}), 128.39 (C-3_{phenyl} and C-5_{phenyl}), 106.50 (C-7), 103.81 (C-4), 61.39 (CO*C*H_2N), 56.61 (C_{benzyl}), 56.47 (OMe), 56.24 (OMe), 53.62 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.80 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 46.51 (C-1), 45.01 (C-2). HRMS: calculated (491.1378), found (491.1437).

*6.4.11. 2-(4-Benzylpiperazin-1-yl)-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl) acetamide (**12**)*

Yield: 50%. M.P. 211 °C. IR (KBr, cm^{-1}): 3373 (NH), 1717 (CO), 1661 (CO amide), 2813, 1510, 1092, 1007, 699. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.56 (d, $^3J_{NH-H4c}$ = 8.2 Hz, 1H,NH), 7.28 (m, 5H, H_{phenyl}), 5.36 (dt, $^3J_{H4c-H5a}$ = 3.8 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.2 Hz, 1H, H-4c), 3.51 (m, 3H, H_{benzyl} and H-5b), 3.06 (s, 2H, CO*C*H_2N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.8 Hz, $^2J_{H5a-H5b}$ = 19.4 Hz, 1H, H-5a), 2.55 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.35 (C-6), 170.23 (NHCO), 151.68 (C-6a), 141.95 (C-3a), 137.55 (C-1_{phenyl}), 129.31 (C-2_{phenyl} and C-6_{phenyl}), 128.30 (C-3_{phenyl} and C-5_{phenyl}), 127.22 (C-4_{phenyl}), 111.95 (C-1), 106.01 (C-3), 62.84 (C_{benzyl}), 61.33 (CO*C*H_2N), 53.65 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.94 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.15 (C-5), 43.04 (C-4). MS (m/z): 529.1 ($^+$M+2), 527.1 ($^+$M), 525.1 ($^+$M–2). Anal. CHN $C_{20}H_{21}Br_2N_3O_2S$.

*6.4.12. 2-[4-(2-Chlorobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**13**)*

Yield: 77%. M.P. 170 °C. IR (KBr, cm^{-1}): 3284 (NH), 1717 (CO), 1661 (CO amide), 2811, 1503, 1469, 1131, 1011, 753. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.59 (d, $^3J_{NH-H4c}$ = 8.1 Hz, 1H,NH), 7.35 (d, $^3J_{H3phenyl-H4phenyl}$ = 7.6 Hz, 1H, H-3_{phenyl}), 7.24 (d, $^3J_{H6phenyl-H5phenyl}$ = 7.2 Hz, 1H, H-6_{phenyl}), 7.19 (m, 2H, H-4_{phenyl} and H-5_{phenyl}), 5.27 (dt, $^3J_{H4c-H5a}$ = 3.6 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.1 Hz, 1H, H-4c), 3.52 (s, 2H, H_{benzyl}), 3.28 (dd, $^3J_{H5b-H4c}$ = 8.1 Hz, $^2J_{H5b-H5a}$ = 20.0 Hz, 1H, H-5b), 2.97 (s, 2H, CO*C*H_2N), 2.73 (dd, $^3J_{H5a-H4c}$ = 3.6 Hz, $^2J_{H5a-H5b}$ = 20.0 Hz, 1H, H-5a), 2.45 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.26 (C-6), 170.14 (NHCO), 151.62 (C-6a), 141.88 (C-3a), 135.50 (C-1_{phenyl}), 134.20 (C-2_{phenyl}), 130.58 (C-6_{phenyl}), 129.39 (C-3_{phenyl}), 128.16 (C-4_{phenyl}), 126.57 (C-5_{phenyl}), 111.80 (C-1), 105.91 (C-3), 61.26 (CO*C*H_2N), 58.92 (C_{benzyl}), 53.62 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.93 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.05 (C-5), 42.99 (C-4). MS (m/z): 563.0 ($^+$M+2), 561.0 ($^+$M), 559.0 ($^+$M–2). Anal. CHN $C_{20}H_{20}Br_2ClN_3O_2S$.

*6.4.13. 2-[4-(3-Chlorobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**14**)*

Yield: 66%. M.P. 195 °C. IR (KBr, cm^{-1}): 3374 (NH), 1718 (CO), 1662 (CO amide), 2890, 1509, 1476, 1129, 1008, 779. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.57 (d, $^3J_{NH-H4c}$ = 8.0 Hz, 1H,NH), 7.23 (m, 4H, H_{phenyl}), 5.37 (dt, $^3J_{H4c-H5a}$ = 3.7 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.0 Hz, 1H, H-4c), 3.52 (dd, $^3J_{H5b-H4c}$ = 8.0 Hz, $^2J_{H5b-H5a}$ = 19.2 Hz, 1H, H-5b), 3.45 (s, 2H, H_{benzyl}), 3.06 (s, 2H, CO*C*H_2N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.7 Hz, $^2J_{H5a-H5b}$ = 19.2 Hz, 1H, H-5a), 2.56 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.36 (C-6), 170.15 (NHCO), 151.66 (C-6a), 141.93 (C-3a), 140.00 (C-3_{phenyl}), 134.21 (C-1_{phenyl}), 129.55 (C-5_{phenyl}), 128.94 (C-2_{phenyl}), 127.36 (C-6_{phenyl}), 127.08 (C-4_{phenyl}), 111.92 (C-1), 105.99 (C-3), 62.17 (CO*C*H_2N), 61.29 (C_{benzyl}), 53.59 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.93 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.13 (C-5), 43.03 (C-4). MS (m/z): 563.0 ($^+$M+2), 561.0 ($^+$M), 559.0 ($^+$M–2).

*6.4.14. 2-[4-(4-Chlorobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**15**)*

Yield: 30%. M.P. 192 °C. IR (KBr, cm^{-1}): 3369 (NH), 1717 (CO), 1661 (CO amide), 2812, 1510, 1334, 1130, 1008, 807. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.57 (d, $^3J_{NH\text{-}H4c}$ = 8.0 Hz, 1H,NH), 7.27 (m, 4H, H_{phenyl}), 5.36 (dt, $^3J_{H4c\text{-}H5a}$ = 3.7 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.0 Hz, 1H, H-4c), 3.50 (dd, $^3J_{H5b\text{-}H4c}$ = 8.0 Hz, $^2J_{H5b\text{-}H5a}$ = 19.4 Hz, 1H, H-5b), 3.46 (s, 2H, H_{benzyl}), 3.06 (s, 2H, COCH_2N), 2.82 (dd, $^3J_{H5a\text{-}H4c}$ = 3.7 Hz, $^2J_{H5a\text{-}H5b}$ = 19.4 Hz, 1H, H-5a), 2.56 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.36 (C-6), 170.15 (NHCO), 151.66 (C-6a), 141.91 (C-3a), 136.39 (C-1_{phenyl}), 132.85 (C-4_{phenyl}), 130.31 (C-2_{phenyl} and C-6_{phenyl}), 128.41 (C-3_{phenyl} and C-5_{phenyl}), 111.89 (C-1), 105.98 (C-3), 61.99 (COCH_2N), 61.28 (C_{benzyl}), 53.60 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.87 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.10 (C-5), 43.00 (C-4). MS (m/z): 563.0 ($^+$M+2), 561.0 ($^+$M), 559.0 ($^+$M–2). Anal. CHN $C_{20}H_{20}Br_2ClN_3O_2S$.

*6.4.15. 2-[4-(2,3-Dichlorobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta [c]thien-4-yl)-acetamide (**16**)*

Yield: 60%. M.P. 181 °C. IR (KBr, cm^{-1}): 3437 (NH), 1721 (CO), 1667 (CO amide), 2818, 1508, 1132, 1011, 777. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.59 (d, $^3J_{NH\text{-}H4c}$ = 8.1 Hz, 1H,NH), 7.34 (d, $^3J_{H4phenyl\text{-}H5phenyl}$ = 7.8 Hz, 1H, H-4_{phenyl}), 7.31 (d, $^3J_{H6phenyl\text{-}H5phenyl}$ = Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.1 Hz, 1H, H-4c), 3.58 (s, 2H, H_{benzyl}), 3.45 (dd, $^3J_{H5b\text{-}H4c}$ = 8.1 Hz, $^2J_{H5b\text{-}H5a}$ = 19.3 Hz,7.8 Hz, 1H, H-6_{phenyl}), 7.13 (t, $^3J_{H5phenyl\text{-}H4phenyl}$ = $^3J_{H5phenyl\text{-}H6phenyl}$ = 7.8 Hz, 1H, H-5_{phenyl}), 5.32 (dt, $^3J_{H4c\text{-}H5a}$ = 3.8 1H, H-5b), 3.02 (s, 2H, COCH_2N), 2.79 (dd, $^3J_{H5a\text{-}H4c}$ = 3.8 Hz, $^2J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.56 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.29 (C-6), 170.08 (NHCO), 151.59 (C-6a), 141.85 (C-3a), 138.05 (C-1_{phenyl}), 132.99 (C-3_{phenyl}), 132.21 (C-2_{phenyl}), 128.91 (C-4_{phenyl}), 128.38 (C-6_{phenyl}), 126.96 (C-5_{phenyl}), 111.82 (C-1), 105.91(C-3), 61.24 (COCH_2N), 59.62 (C_{benzyl}), 53.60 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.98 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.03 (C-5), 42.97 (C-4). MS (m/z): 596.9 ($^+$M+2), 594.9 ($^+$M), 592.9 ($^+$M–2).

*6.4.16. 2-[4-(2,4-Dichlorobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta [c]thien-4-yl)-acetamide (**17**)*

Yield: 25%. M.P. 195 °C. IR (KBr, cm^{-1}): 3425 (NH), 1721 (CO), 1659 (CO amide), 2925, 1468, 1199, 1195, 812. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.51 (d, $^3J_{NH\text{-}H4c}$ = 8.2 Hz, 1H,NH), 7.32 (d, $^3J_{H5phenyl\text{-}H6phenyl}$ = 7.8 Hz, 1H, H-5_{phenyl}), 7.2 (s, 1H, H-3_{phenyl}), 7.13 (d, $^3J_{H6phenyl\text{-}H5phenyl}$ = 7.8 Hz, 1H, H-6_{phenyl}), 5.30 (dt, $^3J_{H4c\text{-}H5a}$ = 3.6 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.2 Hz, 1H, H-4c), 3.50 (s, 2H, H_{benzyl}), 3.44 (dd, $^3J_{H5b\text{-}H4c}$ = 8.2 Hz, $^2J_{H5b\text{-}H5a}$ = 19.3 Hz, 1H, H-5b), 3.00 (s, 2H, COCH_2N), 2.79 (dd, $^3J_{H5a\text{-}H4c}$ = 3.6 Hz, $^2J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.56 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.30 (C-6), 170.14 (NHCO), 151.64 (C-6a), 141.94 (C-3a), 134.82 (C-1_{phenyl}), 134.27 (C-2_{phenyl}), 133.24 (C-4_{phenyl}), 131.91 (C-6_{phenyl}), 129.27 (C-3_{phenyl}), 126.98 (C-5_{phenyl}), 111.97 (C-1), 105.97 (C-3), 61.29 (COCH_2N), 58.40 (C_{benzyl}), 53.65 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.95 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.14 (C-5), 43.07 (C-4). MS (m/z): 596.9 ($^+$M+2), 594.9 ($^+$M), 592.9 ($^+$M–2).

*6.4.17. 2-[4-(2,5-Dichlorobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta [c]thien-4-yl)-acetamide (**18**)*

Yield: 50%. M.P. 195 °C. IR (KBr, cm^{-1}): 3341 (NH), 1728 (CO), 1670 (CO amide), 2817, 1507, 1472, 1132, 1012, 811. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.51 (d, $^3J_{NH\text{-}H4c}$ = 8.0 Hz, 1H,NH), 7.46 (d, $^4J_{H6phenyl\text{-}H4phenyl}$ = 2.4 Hz, 1H, H-6_{phenyl}), 7.26 (d, $^3J_{H3phenyl\text{-}H4phenyl}$ = 8.5 Hz, 1H, H-3_{phenyl}), 7.16 (dd, $^4J_{H4phenyl\text{-}H6phenyl}$ = 2.4 Hz, $^3J_{H4phenyl\text{-}H3phenyl}$ = 8.5 Hz, 1H, H-4_{phenyl}), 5.36 (dt, $^3J_{H4c\text{-}H5a}$ = 3.6 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.0 Hz, 1H, H-4c), 3.58 (s, 2H, H_{benzyl}), 3.51 (dd, $^3J_{H5b\text{-}H4c}$ = 8.0 Hz, $^2J_{H5b\text{-}H5a}$ = 19.3 Hz, 1H, H-5b), 3.07 (s, 2H, COCH_2N), 2.84 (dd, $^3J_{H5a\text{-}H4c}$ = 3.6 Hz, $^2J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.58 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.31 (C-6), 170.16 (NHCO), 151.66 (C-6a), 141.96 (C-3a), 137.59 (C-1_{phenyl}), 132.73 (C-5_{phenyl}), 132.29 (C-2_{phenyl}), 130.52 (C-3_{phenyl}), 130.18 (C-6_{phenyl}), 128.23 (C-4_{phenyl}), 111.97 (C-1), 105.99 (C-3), 61.30 (COCH_2N), 58.69 (C_{benzyl}), 53.66 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 53.06 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.17 (C-5), 43.09 (C-4). MS (m/z): 515.9 ($^+$M+1-Br), 513.9 ($^+$M–1-Br).

*6.4.18. 2-[4-(2,6-Dichlorobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta [c]thien-4-yl)-acetamide (**19**)*

Yield: 68%. M.P. 245 °C. IR (KBr, cm^{-1}): 3338 (NH), 1708 (CO), 1653 (CO amide), 2817, 1472, 1135, 1006, 762. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.64 (d, $^3J_{NH\text{-}H4c}$ = 8.0 Hz, 1H,NH), 7.29 (d, $^3J_{H3phenyl\text{-}H4phenyl}$ = $^3J_{H5phenyl\text{-}H4phenyl}$ = 7.7 Hz, 2H, H-3_{phenyl} and H-5_{phenyl}), 7.16 (t, $^3J_{H4phenyl\text{-}H3phenyl}$ = $^3J_{H4phenyl\text{-}H5phenyl}$ = 7.7 Hz, 1H, H-4_{phenyl}), 5.36 (m, 1H, H-4c), 3.74 (s, 2H, H_{benzyl}), 3.44 (dd, $^3J_{H5b\text{-}H4c}$ = 7.9 Hz, $^2J_{H5b\text{-}H5a}$ = 18.9 Hz, 1H, H-5b), 3.00 (s, 2H, COCH_2N), 2.79 (dd, $^3J_{H5a\text{-}H4c}$ = 3.6 Hz, $^2J_{H5a\text{-}H5b}$ = 18.9 Hz, 1H, H-5a), 2.58 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.42 (C-6), 170.35 (NHCO), 151.66 (C-6a), 141.97 (C-3a), 136.93 (C-2_{phenyl} and C-6_{phenyl}), 134.04 (C-1_{phenyl}), 128.94 (C-4_{phenyl}), 128.38 (C-3_{phenyl} and C-5_{phenyl}), 111.92 (C-1), 106.00 (C-3), 61.27 (COCH_2N), 56.25 (C_{benzyl}), 53.67 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.87 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.15 (C-5), 43.07 (C-4).). MS (m/z): 596.5 ($^+$M+2), 594.5 ($^+$M), 592.5 ($^+$M–2).

*6.4.19. 2-[4-(2-Fluorobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**20**)*

Yield: 50%. M.P. 185 °C. IR (KBr, cm^{-1}): 3370 (NH), 1718 (CO), 1660 (CO amide), 2935, 1510, 1216, 1192, 1044, 754.

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.55 (d, $^3J_{NH\text{-}H4c}$ = 8.2 Hz, 1H,NH), 7.36 (dt, $^4J_{H6phenyl\text{-}H4phenyl}$ = 1.7 Hz, $^4J_{H6phenyl\text{-}F}$ = $^3J_{H6phenyl\text{-}H5phenyl}$ = 7.5 Hz, 1H, H-6$_{phenyl}$), 7.22 (m, 1H, H-4$_{phenyl}$), 7.10 (t, $^3J_{H5phenyl\text{-}H4phenyl}$ = $^3J_{H5phenyl\text{-}H6phenyl}$ = 7.5 Hz, 1H, H-5$_{phenyl}$), 7.02 (t, $^3J_{H3phenyl\text{-}H4phenyl}$ = $^3J_{H3phenyl\text{-}F}$ = 9.2 Hz, 1H, H-3$_{phenyl}$), 5.35 (dt, $^3J_{H4c\text{-}H5a}$ = 3.5 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.2 Hz, 1H, H-4c), 3.59 (s, 2H, H$_{benzyl}$), 3.50 (dd, $^3J_{H5b\text{-}H4c}$ = 8.2 Hz, $^2J_{H5b\text{-}H5a}$ = 19.4 Hz, 1H, H-5b), 3.05 (s, 2H, COCH_2N), 2.82 (dd, $^3J_{H5a\text{-}H4c}$ = 3.5 Hz, $^2J_{H5a\text{-}H5b}$ = 19.4 Hz, 1H, H-5a), 2.60 (m, 8H, H$_{piperazine}$). ^{13}C-NMR (DMSO-d6) δ (ppm): 191.92 (C-6), 169.68 (NHCO), 160.84 (d, $^1J_{C\text{–}F}$, = 246.2 Hz, C-2$_{phenyl}$), 151.27 (C-6a), 141.43 (C-3a), 131.03 (d, $^3J_{C\text{–}F}$ = 5.0 Hz, C-6$_{phenyl}$), 128.40 (d, $^3J_{C\text{–}F}$ = 8.3 Hz, C-4$_{phenyl}$), 123.73 (d, $^2J_{C\text{–}F}$ = 14.8 Hz, C-1$_{phenyl}$), 123.42 (d, $^4J_{C\text{–}F}$ = 3.3 Hz, C-5$_{phenyl}$), 114.76 ($^2J_{C\text{–}F}$ = 22.3 Hz,C-3$_{phenyl}$), 111.20 (C-1), 105.49 (C-3), 60.83 (COCH_2N), 54.49 (C$_{benzyl}$), 53.09 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.13 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 51.50 (C-5), 42.46 (C-4). MS (m/z): 547.3 ($^+$M+2), 545.3 ($^+$M), 543.3 ($^+$M–2). Anal. CHN $C_{20}H_{20}Br_2FN_3O_2S$.

*6.4.20. 2-[4-(3-Fluorobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**21**)*

Yield: 71%. M.P. 192 °C. IR (KBr, cm^{-1}): 3376 (NH), 1716 (CO), 1661 (CO amide), 2816, 1510, 1478, 1255, 1092, 797. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.54 (d, $^3J_{NH\text{-}H4c}$ = 8.2 Hz, 1H,NH), 7.29-6.92 (m, 4H, H$_{phenyl}$), 5.36 (dt, $^3J_{H4c\text{-}H5a}$ = 3.7 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.2 Hz, 1H, H-4c), 3.50 (m, 3H, H$_{benzyl}$ and H-5b), 3.06 (s, 2H, COCH_2N), 2.82 (dd, $^3J_{H5a\text{-}H4c}$ = 3.7 Hz, $^2J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.60 (m, 8H, H$_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.29 (C-6), 170.11 (NHCO), 162.99 (d, $^1J_{C\text{–}F}$ = 245.3 Hz, C-3$_{phenyl}$), 151.69 (C-6a), 141.98 (C-3a), 140.59 (d, $^3J_{C\text{–}F}$ = 6.6 Hz, C-1$_{phenyl}$), 129.74 (d, $^3J_{C\text{–}F}$ = 7.4 Hz, C-5$_{phenyl}$), 124.48 (d, $^4J_{C\text{–}F}$ = 2.5 Hz, C-6$_{phenyl}$), 115.71 (d, $^2J_{C\text{–}F}$ = 21.4 Hz, C-4$_{phenyl}$), 114.13 (d, $^2J_{C\text{–}F}$ = 20.7 Hz, C-2$_{phenyl}$), 111.96 (C-1), 106.00 (C-3), 62.19 (C$_{benzyl}$), 61.31 (COCH_2N), 53.59 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.93 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 52.16 (C-5), 43.09 (C-4). MS (m/z): 546.5 ($^+$M+2), 544.5 ($^+$M), 542.5 ($^+$M–2).

*6.4.21. 2-[4-(4-Fluorobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**22**)*

Yield: 79%. M.P. 176 °C. IR (KBr, cm^{-1}): 3372 (NH), 1716 (CO), 1662 (CO amide), 2811, 1510, 1476, 1222, 1129, 822. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.54 (d, $^3J_{NH\text{-}H4c}$ = 8.0 Hz, 1H,NH), 7.28 (m, 2H, H-2$_{phenyl}$ and H-6$_{phenyl}$), 6.98 (t, $^3J_{H3phenyl\text{-}H2phenyl}$ = $^3J_{H5phenyl\text{-}H6phenyl}$ = $^3J_{H3phenyl\text{-}F}$ = $^3J_{H5phenyl\text{-}F}$ = 8.6 Hz, 2H, H-3$_{phenyl}$ and H-5$_{phenyl}$), 5.36 (dt, $^3J_{H4c\text{-}H5a}$ = 3.6 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.0 Hz, 1H, H-4c), 3.51 (m, 3H, H$_{benzyl}$ and H-5b), 3.06 (s, 2H, COCH_2N), 2.82 (dd, $^3J_{H5a\text{-}H4c}$ = 3.6 Hz, $^2J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.54 (m, 8H, H$_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.29 (C-6), 170.17 (NHCO), 162.10 (d, $^1J_{C\text{–}F}$ = 244.6 Hz, C-4$_{phenyl}$), 151.72 (C-6a), 141.99 (C-3a), 133.60 (d, $^4J_{C\text{–}F}$ = 3.3 Hz, C-1$_{phenyl}$), 130.52 (d, $^3J_{C\text{–}F}$ = 8.2 Hz, C-2$_{phenyl}$ and C-6$_{phenyl}$), 115.11 (d, $^2J_{C\text{–}F}$ = 21.4 Hz, C-3$_{phenyl}$ and C-5$_{phenyl}$), 111.95 (C-1), 106.00 (C-3), 62.02 (C$_{benzyl}$), 61.34 (COCH_2N), 53.66 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.90 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 52.18 (C-5), 43.09 (C-4). MS (m/z): 546.5 ($^+$M+2), 544.5 ($^+$M), 542.5 ($^+$M–2).

*6.4.22. 2-[4-(2-Bromobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**23**)*

Yield: 79%. M.P. 176 °C. IR (KBr, cm^{-1}): 3333 (NH), 1722 (CO), 1666 (CO amide), 2813, 1502, 1132, 1011, 752. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.64 (d, $^3J_{NH\text{-}H4c}$ = 8.1 Hz, 1H,NH), 7.52 (dd, $^4J_{H3phenyl\text{-}H5phenyl}$ = 1.3 Hz, $^3J_{H3phenyl\text{-}H4phenyl}$ = 7.3 Hz, 1H, H-3$_{phenyl}$), 7.44 (d, $^3J_{H6phenyl\text{-}H5phenyl}$ = 7.3 Hz, 1H, H-6$_{phenyl}$), 7.27 (t, $^3J_{H4phenyl\text{-}H5phenyl}$ = $^3J_{H4phenyl\text{-}H3phenyl}$ = 7.3 Hz, 1H, H-4$_{phenyl}$), 7.10 (dt, $^4J_{H5phenyl\text{-}H3phenyl}$ = 1.3 Hz, $^3J_{H5phenyl\text{-}H4phenyl}$ = $^3J_{H5phenyl\text{-}H6phenyl}$ = 7.3 Hz, 1H, H-5$_{phenyl}$), 5.36 (dt, $^3J_{H4c\text{-}H5a}$ = 3.7 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.1 Hz, 1H, H-4c), 3.53 (s, 2H, H$_{benzyl}$), 3.48 (dd, $^3J_{H5b\text{-}H4c}$ = 8.1 Hz, $^2J_{H5b\text{-}H5a}$ = 19.3 Hz, 1H, H-5b), 3.06 (s, 2H, COCH_2N), 2.83 (dd, $^3J_{H5a\text{-}H4c}$ = 3.7 Hz, $^2J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.59 (m, 8H, H$_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.30 (C-6), 170.15 (NHCO), 151.68 (C-6a), 141.90 (C-3a), 137.20 (C-1$_{phenyl}$), 132.70 (C-3$_{phenyl}$), 130.63 (C-4$_{phenyl}$), 128.47 (H-6$_{phenyl}$), 127.22 (C-5$_{phenyl}$), 124.57 (C-2$_{phenyl}$), 111.74 (C-1), 105.93 (C-3), 61.48 (C$_{benzyl}$), 61.29 (COCH_2N), 53.64 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.93 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 52.04 (C-5), 42.99 (C-4). MS (m/z): 608.3 ($^+$M+3), 606.3 ($^+$M+1), 604.3 ($^+$M–1), 602.3 ($^+$M-3). Anal. CHN $C_{20}H_{20}Br_3N_3O_2S$.

*6.4.23. 2-[4-(2-Iodobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**24**)*

Yield: 66%. M.P. 175 °C. IR (KBr, cm^{-1}): 3424 (NH), 1719 (CO), 1655 (CO amide), 2818, 1511, 1127, 1006, 750. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.83 (dd, $^4J_{H3phenyl\text{-}H5phenyl}$ = 1.0 Hz, $^3J_{H3phenyl\text{-}H4phenyl}$ = 7.7 Hz, 1H, H-3$_{phenyl}$), 7.60 (d, $^3J_{NH\text{-}H4c}$ = 8.2 Hz, 1H,NH), 7.38 (dd, $^4J_{H6phenyl\text{-}H4phenyl}$ = 1.7 Hz, $^3J_{H6phenyl\text{-}H5phenyl}$ = 7.7 Hz, 1H, H-6$_{phenyl}$), 7.30 (dt, $^4J_{H5phenyl\text{-}H3phenyl}$ = 1.0 Hz, $^3J_{H5phenyl\text{-}H4phenyl}$ = $^3J_{H5phenyl\text{-}H3phenyl}$ = 7.7 Hz, 1H, H-5$_{phenyl}$), 6.95 (dt, $^4J_{H4phenyl\text{-}H6phenyl}$ = 1.7 Hz, $^3J_{H4phenyl\text{-}H5phenyl}$ = $^3J_{H4phenyl\text{-}H3phenyl}$ = 7.7 Hz, 1H, H-4$_{phenyl}$), 5.37 (dt, $^3J_{H4c\text{-}H5a}$ = 3.7 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.2 Hz, 1H, H-4c), 3.53 (m, 3H, H$_{benzyl}$ and H-5b), 3.07 (s, 2H, COCH_2N), 2.84 (dd, $^3J_{H5a\text{-}H4c}$ = 3.7 Hz, $^2J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.45 (m, 8H, H$_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.36 (C-6), 170.21 (NHCO), 151.60 (C-6a), 141.90 (C-3a), 140.18 (C-1$_{phenyl}$), 139.49 (C-3$_{phenyl}$), 130.21 (C-5$_{phenyl}$), 128.78 (C-4$_{phenyl}$), 128.01 (C-6$_{phenyl}$), 111.92 (C-1), 106.00 (C-3), 100.55 (C-2$_{phenyl}$), 66.21 (C$_{benzyl}$), 61.28 (COCH_2N), 53.68 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.84 (C-2$_{piperazine}$ and

C-6$_{piperazine}$), 52.11 (C-5), 43.01 (C-4). MS (m/z): 573.9 ($^+$M+1-Br), 571.9 ($^+$M–1-Br). Anal. CHN $C_{20}H_{20}Br_2IN_3O_2S$.

*6.4.24. 2-[4-(2-Trifluorometheylbenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl)acetamide (**25**)*

Yield: 30%. M.P. 130 °C. IR (KBr, cm^{-1}): 3429 (NH), 1718 (CO), 1666 (CO amide), 2814, 1508, 1313, 1117, 770. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.76 (d, $^3J_{NH\text{-}H4c}$ = 7.6 Hz, 1H,NH), 7.64 (d, $^3J_{H3phenyl\text{-}H4phenyl}$ = 7.5 Hz, 1H, H-3$_{phenyl}$), 7.60 (d, $^3J_{H6phenyl\text{-}H5phenyl}$ = 7.5 Hz, 1H, H-6$_{phenyl}$), 7.51 (t, $^3J_{H4phenyl\text{-}H5phenyl}$ = $^3J_{H4phenyl\text{-}H3phenyl}$ = 7.5 Hz, 1H, H-4$_{phenyl}$), 7.33 (t, $^3J_{H5phenyl\text{-}H4phenyl}$ = $^3J_{H5phenyl\text{-}H6phenyl}$ = 7.5 Hz, 1H, H-5$_{phenyl}$), 5.36 (dt, $^3J_{H4c\text{-}H5a}$ = 3.7 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 7.6 Hz, 1H, H-4c), 3.66 (s, 2H, H$_{benzyl}$), 3.49 (dd, $^3J_{H5b\text{-}H4c}$ = 7.6 Hz, $^2J_{H5b\text{-}H5a}$ = 19.3 Hz, 1H, H-5b), 3.07 (s, 2H, COC*H$_2$*N), 2.84 (dd, $^3J_{H5a\text{-}H4c}$ = 3.7 Hz, $^2J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.59 (m, 8H, H$_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.22 (C-6), 170.02 (NHCO), 151.59 (C-6a), 141.82 (C-3a), 137.23 (C-1$_{phenyl}$), 131.68 (C-5$_{phenyl}$), 130.16 (C-6$_{phenyl}$), 128.40 (q, $^2J_{C\text{–}F}$ = 30.1 Hz, C-2$_{phenyl}$), 126.77 (C-4$_{phenyl}$), 125.62 (C-3$_{phenyl}$), 124.18 (q, $^1J_{C\text{–}F}$ = 292.9 Hz, CF_3), 111.64 (C-1), 105.84 (C-3), 61.20 (CO*C*H$_2$N), 57.82 (C$_{benzyl}$), 53.55 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.93 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 51.91 (C-5), 42.92 (C-4). MS (m/z): 598.0 ($^+$M+2), 596.0 ($^+$M), 594.0 ($^+$M–2). Anal. CHN $C_{21}H_{20}Br_2F_3N_3O_2S$.

*6.4.25. 2-[4-(2-Methylylbenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**26**)*

Yield: 65%. M.P. 175 °C. IR (KBr, cm^{-1}): 3372 (NH), 1720 (CO), 1658 (CO amide), 2813, 1511, 1130, 1007, 741. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.62 (d, $^3J_{NH\text{-}H4c}$ = 8.1 Hz, 1H,NH), 7.20 (m, 4H, H$_{phenyl}$), 5.36 (dt, $^3J_{H4c\text{-}H5a}$ = 3.7 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.1 Hz, 1H, H-4c), 3.50 (dd, $^3J_{H5b\text{-}H4c}$ = 8.1 Hz, $^2J_{H5b\text{-}H5a}$ = 19.4 Hz, 1H, H-5b), 3.45 (s, 2H, H$_{benzyl}$), 3.04 (s, 2H, COC*H$_2$*N), 2.82 (dd, $^3J_{H5a\text{-}H4c}$ = 3.7 Hz, $^2J_{H5a\text{-}H5b}$ = 19.4 Hz, 1H, H-5a), 2.55 (m, 8H, H$_{piperazine}$), 2.34 (s, 3H, Me). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.35 (C-6), 170.26 (NHCO), 151.71 (C-6a), 141.94 (C-3a), 137.53 (C-2$_{phenyl}$), 136.06 (C-1$_{phenyl}$), 130.30 (C-3$_{phenyl}$), 129.76 (H-6$_{phenyl}$), 127.15 (C-4$_{phenyl}$), 125.48 (C-5$_{phenyl}$), 111.85 (C-1), 105.98 (C-3), 61.32 (C$_{benzyl}$), 60.68 (CO*C*H$_2$N), 53.77 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 53.03 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 52.13 (C-5), 43.03 (C-4), 19.21 (Me). MS (m/z): 543.0 ($^+$M+2), 541.0 ($^+$M), 539.0 ($^+$M–2). Anal. CHN $C_{21}H_{23}Br_2N_3O_2S$.

*6.4.26. 2-[4-(3-Methylbenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**27**)*

Yield: 67%. M.P. 170 °C. IR (KBr, cm^{-1}): 3367 (NH), 1716 (CO), 1660 (CO amide), 2814, 1514, 1133, 1094, 1007, 773. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.62 (d, $^3J_{NH\text{-}H4c}$ = 8.2 Hz, 1H,NH), 7.19 (t, $^3J_{H5phenyl\text{-}H4phenyl}$ = $^3J_{H5phenyl\text{-}H6phenyl}$ = 7.4 Hz, 1H, H-5$_{phenyl}$), 7.11 (s, 1H, H-2$_{phenyl}$), 7.09 (d, $^3J_{H6phenyl\text{-}H5phenyl}$ = 7.4 Hz, 1H, H-6$_{phenyl}$), 7.05 (d, $^3J_{H4phenyl\text{-}H5phenyl}$ = 7.4 Hz, 1H, H-4$_{phenyl}$), 5.36 (dt, $^3J_{H4c\text{-}H5a}$ = 3.8 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.2 Hz, 1H, H-4c), 3.47 (m, 3H, H$_{benzyl}$ and H-5b), 3.05 (s, 2H, COC*H$_2$*N), 2.82 (dd, $^3J_{H5a\text{-}H4c}$ = 3.8 Hz, $^2J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.55 (m, 8H, H$_{piperazine}$), 2.33 (s, 3H, Me). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.30 (C-6), 170.19 (NHCO), 151.73 (C-6a), 141.94 (C-3a), 137.86 (C-1$_{phenyl}$), 137.60 (C-3$_{phenyl}$), 129.82 (C-2$_{phenyl}$), 128.12 (C-5$_{phenyl}$), 127.92 (C-6$_{phenyl}$), 126.20 (C-4$_{phenyl}$), 111.77 (C-1), 105.97 (C-3), 62.82 (C$_{benzyl}$), 61.32 (CO*C*H$_2$N), 53.61 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.93 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 52.06 (C-5), 43.02 (C-4), 21.37 (Me). MS (m/z): 542.5 ($^+$M+2), 540.5 ($^+$M), 538.5 ($^+$M–2).

*6.4.27. 2-[4-(4-Methylbenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**28**)*

Yield: 77%. M.P. 181 °C. IR (KBr, cm^{-1}): 3372 (NH), 1720 (CO), 1662 (CO amide), 2809, 1510, 1476, 1129, 1007, 838. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.58 (d, $^3J_{NH\text{-}H4c}$ = 8.1 Hz, 1H,NH), 7.18 (d, $^3J_{H3phenyl\text{-}H2phenyl}$ = $^3J_{H5phenyl\text{-}H6phenyl}$ = 8.0 Hz, 2H, H-3$_{phenyl}$ and H-5$_{phenyl}$), 7.11 (d, $^3J_{H2phenyl\text{-}H3phenyl}$ = $^3J_{H6phenyl\text{-}H5phenyl}$ = 8.0 Hz, 2H, H-2$_{phenyl}$ and H-6$_{phenyl}$), 5.35 (dt, $^3J_{H4c\text{-}H5a}$ = 3.7 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.1 Hz, 1H, H-4c), 3.47 (m, 3H, H$_{benzyl}$ and H-5b), 3.05 (s, 2H, COC*H$_2$*N), 2.82 (dd, $^3J_{H5a\text{-}H4c}$ = 3.7 Hz, $^2J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.55 (m, 8H, H$_{piperazine}$), 2.33 (s, 3H, Me). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.31 (C-6), 170.19 (NHCO), 151.72 (C-6a), 141.95 (C-3a), 136.78 (C-1$_{phenyl}$), 134.64 (C-4$_{phenyl}$), 129.08 (C-3$_{phenyl}$ and C-5$_{phenyl}$), 128.94 (C-2$_{phenyl}$ and C-6$_{phenyl}$), 111.81 (C-1), 105.96 (C-3), 62.54 (C$_{benzyl}$), 61.33 (CO*C*H$_2$N), 53.65 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.86 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 52.09 (C-5), 43.02 (C-4), 21.09 (Me). MS (m/z): 543.2 ($^+$M+2), 541.2 ($^+$M), 539.2 ($^+$M–2).

*6.4.28. 2-[4-(2-Nitrobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**29**)*

Yield: 75%. M.P. 180 °C. IR (KBr, cm^{-1}): 3412 (NH), 1720 (CO), 1664 (CO amide), 1526, 1503, 1469, 1131, 753. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.72 (d, $^3J_{NH\text{-}H4c}$ = 8.1 Hz, 1H,NH), 7.49 (m, 3H, H-3$_{phenyl}$, H-5$_{phenyl}$ and H-6$_{phenyl}$), 7.32 (t, $^3J_{H4phenyl\text{-}H3phenyl}$ = $^3J_{H4phenyl\text{-}H5phenyl}$ = 7.7 Hz, 1H, H-4$_{phenyl}$), 5.27 (dt, $^3J_{H4c\text{-}H5a}$ = 3.7 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.1 Hz, 1H, H-4c), 3.71 (s, 2H, H$_{benzyl}$), 3.41 (dd, $^3J_{H5b\text{-}H4c}$ = 8.1 Hz, $^2J_{H5b\text{-}H5a}$ = 19.3 Hz, 1H, H-5b), 2.97 (s, 2H, COC*H$_2$*N), 2.75 (dd, $^3J_{H5a\text{-}H4c}$ = 3.7 Hz, $^2J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.45 (m, 8H, H$_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.24 (C-6), 170.10 (NHCO), 151.60 (C-6a), 149.75 (C-2$_{phenyl}$), 141.86 (C-3a), 133.38 (C-1$_{phenyl}$), 132.32 (C-5$_{phenyl}$), 130.77 (C-4$_{phenyl}$), 127.98 (C-6$_{phenyl}$), 124.31 (C-3$_{phenyl}$), 111.78 (C-1), 105.87 (C-3), 61.16 (CO*C*H$_2$N), 58.66 (C$_{benzyl}$), 53.52 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.92 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 52.01

(C-5), 43.01 (C-4). MS (m/z): 574.5 ($^+$M+2), 572.5 ($^+$M), 570.5 ($^+$M–2).

*6.4.29. 2-[4-(3-Nitrobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**30**)*

Yield: 100%. M.P. 152 °C. IR (KBr, cm^{-1}): 3368 (NH), 1719 (CO), 1661 (CO amide), 2810, 1612, 1512, 1130, 1008, 842. ^{1}H-NMR (CDCl$_3$) δ (ppm): 8.19 (s, 1H, H-2$_{phenyl}$), 8.11 (d, $^3J_{H4phenyl-H5phenyl}$ = 8.1 Hz, 1H, H-4$_{phenyl}$), 7.66 (d, $^3J_{H6phenyl-H5phenyl}$ = 8.1 Hz, 1H, H-6$_{phenyl}$), 7.53 (d, $^3J_{NH-H4c}$ = 8.1 Hz, 1H,NH), 7.49 (t, $^3J_{H5phenyl-H4phenyl}$ = $^3J_{H5phenyl-H6phenyl}$ = 8.1 Hz, 1H, H-5$_{phenyl}$), 5.36 (dt, $^3J_{H4c-H5a}$ = 3.7 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.1 Hz, 1H, H-4c), 3.59 (s, 2H, H$_{benzyl}$), 3.50 (dd, $^3J_{H5b-H4c}$ = 8.1 Hz, $^2J_{H5b-H5a}$ = 19.3 Hz, 1H, H-5b), 3.08 (s, 2H, COC*H*$_2$N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.7 Hz, $^2J_{H5a-H5b}$ = 19.3 Hz, 1H, H-5a), 2.45 (m, 8H, H$_{piperazine}$). ^{13}C-NMR (CDCl$_3$) δ (ppm): 192.32 (C-6), 170.07 (NHCO), 151.68 (C-6a), 148.43 (C-3$_{phenyl}$), 141.97 (C-3a), 140.47 (C-1$_{phenyl}$), 134.90 (C-6$_{phenyl}$), 129.27 (C-5$_{phenyl}$), 123.66 (C-2$_{phenyl}$), 122.35 (C-4$_{phenyl}$), 111.99 (C-1), 105.99 (C-3), 61.84 (C$_{benzyl}$), 61.29 (CO*C*H$_2$N), 53.57 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 53.00 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 52.16 (C-5), 43.09 (C-4). MS (m/z): 574.5 ($^+$M+2), 572.5 ($^+$M), 570.5 ($^+$M–2).

*6.4.30. 2-[4-(4-Nitrobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**31**)*

Yield: 55%. M.P. 190 °C. IR (KBr, cm^{-1}): 3369 (NH), 1716 (CO), 1660 (CO amide), 2818, 1516, 1348, 1130, 1007, 741. ^{1}H-NMR (CDCl$_3$) δ (ppm): 8.17 (d, $^3J_{H3phenyl-H2phenyl}$ = $^3J_{H5phenyl-H6phenyl}$ = 8.8 Hz, 2H, H-3$_{phenyl}$ and H-5$_{phenyl}$), 7.55 (d, $^3J_{NH-H4c}$ = 8.0 Hz, 1H,NH), 7.50 (d, $^3J_{H2phenyl-H3phenyl}$ = $^3J_{H6phenyl-H5phenyl}$ = 8.8 Hz, 2H, H-2$_{phenyl}$ and H-6$_{phenyl}$), 5.37 (dt, $^3J_{H4c-H5a}$ = 3.6 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.0 Hz, 1H, H-4c), 3.60 (s, 2H, H$_{benzyl}$), 3.51 (dd, $^3J_{H5b-H4c}$ = 8.0 Hz, $^2J_{H5b-H5a}$ = 19.4 Hz, 1H, H-5b), 3.08 (s, 2H, COC*H*$_2$N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.6 Hz, $^2J_{H5a-H5b}$ = 19.4 Hz, 1H, H-5a), 2.58 (m, 8H, H$_{piperazine}$). ^{13}C-NMR (CDCl$_3$) δ (ppm): 192.30 (C-6), 170.03 (NHCO), 151.68 (C-6a), 147.27 (C-4$_{phenyl}$), 146.00 (C-1$_{phenyl}$), 141.97 (C-3a), 129.40 (C-2$_{phenyl}$ and C-6$_{phenyl}$), 123.60 (C-3$_{phenyl}$ and C-5$_{phenyl}$), 111.98 (C-1), 105.98 (C-3), 61.93 (C$_{benzyl}$), 61.31 (CO*C*H$_2$N), 53.60 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 53.08 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 52.17 (C-5), 43.08 (C-4). MS (m/z): 574.0 ($^+$M+2), 572.0 ($^+$M), 570.0 ($^+$M–2).

*6.4.31. 2-[4-(2-Aminobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**32**)*

Yield: 75%. M.P. >240 °C. IR (KBr, cm^{-1}): 3369 (NH), 1720 (CO), 1657 (CO amide), 2804, 1510, 1476, 1135, 747. ^{1}H-NMR (CDCl$_3$) δ (ppm): 7.56 (d, $^3J_{NH-H4c}$ = 8.2 Hz, 1H,NH), 6.90 (m, 4H, H$_{phenyl}$), 5.36 (dt, $^3J_{H4c-H5a}$ = 3.8 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.2 Hz, 1H, H-4c), 3.51 (m, 3H, H$_{benzyl}$ and H-5b), 3.04 (s, 2H, COC*H*$_2$N), 2.81 (dd, $^3J_{H5a-H4c}$ = 3.8 Hz, $^2J_{H5a-H5b}$ = 19.3 Hz, 1H, H-5a), 2.51 (m, 8H, H$_{piperazine}$). ^{13}C-NMR (CDCl$_3$) δ (ppm): 192.36 (C-6), 170.14 (NHCO), 151.60 (C-6a), 146.87 (C-2$_{phenyl}$), 141.94 (C-3a), 130.51 (C-4$_{phenyl}$), 128.57 (C-6$_{phenyl}$), 121.83 (C-1$_{phenyl}$), 117.65 (C-3$_{phenyl}$), 115.55 (C-5$_{phenyl}$), 112.01 (C-1), 106.01 (C-3), 61.81 (C$_{benzyl}$), 61.28 (CO*C*H$_2$N), 53.83 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.64 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 52.14 (C-5), 43.07 (C-4). MS (m/z): 545.0 ($^+$M+2), 543.0 ($^+$M), 541.0 ($^+$M–2).

*6.4.32. 2-[4-(4-Aminobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**33**)*

Yield: 53%. M.P. 130 °C. IR (KBr, cm^{-1}): 3350 (NH), 1720 (CO), 1666 (CO amide), 2811, 1516, 1262, 1131, 802. ^{1}H-NMR (CDCl$_3$) δ (ppm): 7.59 (d, $^3J_{NH-H4c}$ = 8.2 Hz, 1H,NH), 7.06 (d, $^3J_{H2phenyl-H3phenyl}$ = $^3J_{H6phenyl-H5phenyl}$ = 8.3 Hz, 2H, H-2$_{phenyl}$ and H-6$_{phenyl}$), 6.63 (d, $^3J_{H3phenyl-H2phenyl}$ = $^3J_{H5phenyl-H6phenyl}$ = 8.3 Hz, 2H, H-3$_{phenyl}$ and H-5$_{phenyl}$), 5.36 (dt, $^3J_{H4c-H5a}$ = 3.7 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.2 Hz, 1H, H-4c), 3.6 (large, 2H,NH$_2$), 3.48 (dd, $^3J_{H5b-H4c}$ = 8.2 Hz, $^2J_{H5b-H5a}$ = 19.3 Hz, 1H, H-5b), 3.41 (s, 2H, H$_{benzyl}$), 3.04 (s, 2H, COC*H*$_2$N), 2.81 (dd, $^3J_{H5a-H4c}$ = 3.7 Hz, $^2J_{H5a-H5b}$ = 19.3 Hz, 1H, H-5a), 2.53 (m, 8H, H$_{piperazine}$). ^{13}C-NMR (CDCl$_3$) δ (ppm): 192.34 (C-6), 170.24 (NHCO), 151.71 (C-6a), 145.58 (C-4$_{phenyl}$), 141.94 (C-3a), 130.34 (C-2$_{phenyl}$ and C-6$_{phenyl}$), 127.26 (C-1$_{phenyl}$), 114.86 (C-3$_{phenyl}$ and C-5$_{phenyl}$), 111.82 (C-1), 105.97 (C-3), 62.33 (C$_{benzyl}$), 61.32 (CO*C*H$_2$N), 53.62 (C-3$_{piperazine}$ and C-5$_{piperazine}$), 52.76 (C-2$_{piperazine}$ and C-6$_{piperazine}$), 52.08 (C-5), 43.39 (C-4). MS (m/z): 545.1 ($^+$M+2), 543.1 ($^+$M), 541.1 ($^+$M–2).

*6.4.33. 2-[4-(2-Methoxybenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**34**)*

Yield: 60%. M.P. 110 °C. IR (KBr, cm^{-1}): 3430 (NH), 1721 (CO), 1666 (CO amide), 2935, 2815, 1469, 1241, 1132, 755. ^{1}H-NMR (CDCl$_3$) δ (ppm): 7.60 (d, $^3J_{NH-H4c}$ = 8.2 Hz, 1H,NH), 7.32 (dd, $^4J_{H6phenyl-H4phenyl}$ = 1.5 Hz, $^3J_{H6phenyl-H5phenyl}$ = 7.5 Hz, 1H, H-6$_{phenyl}$), 7.25 (dt, $^4J_{H4phenyl-H6phenyl}$ = 1.5 Hz, $^3J_{H4phenyl-H3phenyl}$ = $^3J_{H4phenyl-H5phenyl}$ = 7.5 Hz, 1H, H-4$_{phenyl}$), 6.93 (dt, $^4J_{H5phenyl-H3phenyl}$ = 0.8 Hz, $^3J_{H5phenyl-H4phenyl}$ = $^3J_{H5phenyl-H6phenyl}$ = 7.5 Hz, 1H, H-5$_{phenyl}$), 6.87 (dd, $^4J_{H3phenyl-H5phenyl}$ = 0.8 Hz, $^3J_{H3phenyl-H4phenyl}$ = 7.5 Hz, 1H, H-3$_{phenyl}$), 5.36 (dt, $^3J_{H4c-H5a}$ = 3.7 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.2 Hz, 1H, H-4c), 3.82 (s, 3H, OMe), 3.58 (s, 2H, H$_{benzyl}$), 3.50 (dd, $^3J_{H5b-H4c}$ = 8.2 Hz, $^2J_{H5b-H4c}$ = 19.3 Hz, 1H, H-5b), 3.06 (s, 2H, COC*H*$_2$N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.7 Hz, $^2J_{H5a-H5b}$ = 19.3 Hz, 1H, H-5a), 2.60 (m, 8H, H$_{piperazine}$). ^{13}C-NMR (CDCl$_3$) δ (ppm): 192.35 (C-6), 170.29 (NHCO), 157.78 (C-2$_{phenyl}$), 151.65 (C-6a), 141.92 (C-3a), 130.49 (C-4$_{phenyl}$), 128.15 (C-6$_{phenyl}$), 125.74 (C-1$_{phenyl}$), 120.30 (C-5$_{phenyl}$), 111.86 (C-3$_{phenyl}$), 110.48 (C-1), 105.95 (C-3), 61.30

(CO*C*H_2N), 55.74 (C_{benzyl}), 55.41 (OMe), 53.68 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.86 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.11 (C-5), 43.00 (C-4). MS (m/z): 559.7 ($^+$M+2), 557.7 ($^+$M), 555.7 ($^+$M–2).

*6.4.34. 2-[4-(3-Methoxybenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**35**)*

Yield: 60%. M.P. 148 °C. IR (KBr, cm^{-1}): 3376 (NH), 1716 (CO), 1660 (CO amide), 2934, 2814, 1512, 1262, 1136, 780. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.59 (d, $^3J_{NH-H4c}$ = 8.2 Hz, 1H,NH), 7.23 (t, $^3J_{H5phenyl-H4phenyl}$ = $^3J_{H5phenyl-H6phenyl}$ = 7.9 Hz, 1H, H-5_{phenyl}), 6.88 (m, 2H, H-2_{phenyl} and H-4_{phenyl}), 6.80 (dd, $^4J_{H6phenyl-H4phenyl}$ = 1.8 Hz, $^3J_{H6phenyl-H5phenyl}$ = 7.9 Hz, 1H, H-6_{phenyl}), 5.37 (dt, $^3J_{H4c-H5a}$ = 3.7 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.2 Hz, 1H, H-4c), 3.80 (s, 3H, OMe), 3.50 (m, 3H, H-5b and H_{benzyl}), 3.06 (s, 2H, COC*H_2*N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.7 Hz, $^2J_{H5a-H5b}$ = 19.3 Hz, 1H, H-5a), 2.56 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.21 (C-6), 170.03 (NHCO), 159.40 (C-3_{phenyl}), 151.48 (C-6a), 141.70 (C-3a), 139.29 (C-1_{phenyl}), 129.01 (C-5_{phenyl}), 121.16 (C-6_{phenyl}), 114.36 (C-4_{phenyl}), 112.20 (C-2_{phenyl}), 111.68 (C-1), 105.78 (C-3), 62.52 (C_{benzyl}), 61.10 (CO*C*H_2N), 54.99 (OMe), 53.44 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.71 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 51.88 (C-5), 42.77 (C-4). MS (m/z): 559.3 ($^+$M+2), 557.3 ($^+$M), 555.3 ($^+$M–2).

*6.4.35. 2-[4-(4-Methoxybenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**36**)*

Yield: 44%. M.P. 167 °C. IR (KBr, cm^{-1}): 3330 (NH), 1714 (CO), 1658 (CO amide), 2824, 1526, 1351, 1135, 1010, 735. ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.57 (d, $^3J_{NH-H4c}$ = 8.1 Hz, 1H,NH), 7.20 (d, $^3J_{H2phenyl-H3phenyl}$ = $^3J_{H6phenyl-H5phenyl}$ = 8.2 Hz, 2H, H-2_{phenyl} and H-6_{phenyl}), 6.84 (d, $^3J_{H3phenyl-H2phenyl}$ = $^3J_{H5phenyl-H6phenyl}$ = 8.2 Hz, 2H, H-3_{phenyl} and H-5_{phenyl}), 5.35 (dt, $^3J_{H4c-H5a}$ = 3.4 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.1 Hz, 1H, H-4c), 3.79 (s, 3H, OMe), 3.47 (m, 3H, H-5b and H_{benzyl}), 3.05 (s, 2H, COC*H_2*N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.4 Hz, $^2J_{H5a-H5b}$ = 19.3 Hz, 1H, H-5a), 2.56 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.32 (C-6), 170.23 (NHCO), 158.83 (C-4_{phenyl}), 151.72 (C-6a), 141.96 (C-3a), 130.28 (C-2_{phenyl} and C-6_{phenyl}), 129.80 (C-1_{phenyl}), 113.65 (C-3_{phenyl} and C-5_{phenyl}), 111.86 (C-1), 105.99 (C-3), 62.21 (C_{benzyl}), 61.34 (CO*C*H_2N), 55.25 (OMe), 53.68 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.83 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.13 (C-5), 43.04 (C-4). MS (m/z): 559.7 ($^+$M+2), 557.7 ($^+$M), 555.7 ($^+$M–2).

*6.4.36. 2-[4-(3,4-Dimethoxybenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclo-penta[c]thien-4-yl)-acetamide (**37**)*

Yield: 55%. M.P. 128 °C. IR (KBr, cm^{-1}): 3325 (NH), 1721 (CO), 1669 (CO amide), 2816, 2933, 1514, 1263, 1134, 1027. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.58 (d, $^3J_{NH-H4c}$ = 8.3 Hz, 1H,NH), 6.87 (s, 1H, H-2_{phenyl}), 6.80 (m, 2H, H-5_{phenyl} and H-6_{phenyl}), 5.36 (dt, $^3J_{H4c-H5a}$ = 3.7 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.3 Hz, 1H, Hc), 3.88 (s, 3H, pOMe), 3.87 (s, 3H, mOMe), 3.50 (dd, $^3J_{H5b-H4c}$ = 8.3 Hz, $^2J_{H5b-H4c}$ = 19.4 Hz, 1H, H-5b), 3.44 (s, 2H, H_{benzyl}), 3.06 (s, 2H, COC*H_2*N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.7 Hz, $^2J_{H5a-H5b}$ = 19.4 Hz, 1H, H-5a), 2.54 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.34 (C-6), 170.24 (NHCO), 151.71 (C-6a), 148.94 (C-4_{phenyl}), 148.23 (C-3_{phenyl}), 141.96 (C-3a), 130.47 (C-1_{phenyl}), 121.22 (C-6_{phenyl}), 112.16 (C-5_{phenyl}), 111.91 (C-1), 110.16 (C-2_{phenyl}), 105.99 (C-3), 62.58 (CO*C*H_2N), 61.34 (C_{benzyl}), 55.92 (2OMe), 53.70 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.91 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.14 (C-5), 43.05 (C-4). MS (m/z): 589.0 ($^+$M+2), 587.0 ($^+$M), 585.0 ($^+$M–2).

*6.4.37. 2-[4-(1-Naphthylmethyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**38**)*

Yield: 51%. M.P. 115 °C. IR (KBr, cm^{-1}): 3368 (NH), 1717 (CO), 1660 (CO amide), 2820, 1512, 1134, 750, 466. ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.17 (d, $^3J_{H4naphthalene -H3naphthalene}$ = 8.6 Hz, 1H, H-$4_{naphthalene}$), 7.75 (d, $^3J_{H8naphthalene-H7naphthalene}$ = 5.8 Hz, 1H, H-$8_{naphthalene}$), 7.69 (t, $^3J_{H7naphthalene-H6naphthalene}$ = $^3J_{H7naphthalene -H8naphthalene}$ = 5.8 Hz, 1H, H-$7_{naphthalene}$), 7.55 (d, $^3J_{NH-H4c}$ = 8.1 Hz, 1H,NH), 7.41 (m, 4H, H-$2_{naphthalene}$, H-$3_{naphthalene}$ H-$5_{naphthalene}$, and H-$6_{naphthalene}$), 5.25 (dt, $^3J_{H4c-H5a}$ = 3.6 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.1 Hz, 1H, H-4c), 3.81 (s, 2H,NC*H_2* naphthalene), 3.39 (dd, $^3J_{H5b-H4c}$ = 8.1 Hz, $^2J_{H5b-H5a}$ = 19.3 Hz, 1H, H-5b), 2.95 (s, 2H, COC*H_2*N), 2.73 (dd, $^3J_{H5a-H4c}$ = 3.6 Hz, $^2J_{H5a-H5b}$ = 19.3 Hz, 1H, H-5a), 2.50 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.31 (C-6), 170.19 (NHCO), 151.63 (C-6a), 141.85 (C-3a), 133.75 (C-$1_{naphthalene}$), 133.59 (C-$4a_{naphthalene}$), 132.40 (C-$8a_{naphthalene}$), 128.33 (C-$5_{naphthalene}$), 128.02 (C-$4_{naphthalene}$), 127.32 ($C2_{naphthalene}$), 125.71 (C-$7_{naphthalene}$), 125.60 (C-$3_{naphthalene}$), 125.00 (C-$6_{naphthalene}$), 124.60 (C-$8_{naphthalene}$), 111.78 (C-1), 105.93 (C-3), 61.55 (N*C*H_2 naphthalene), 60.90 (CO*C*H_2N), 53.64 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 53.08 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.03 (C-5), 42.93 (C-4). MS (m/z): 579.3 ($^+$M+2), 577.3 ($^+$M), 575.3 ($^+$M–2).

*6.4.38. 2-[4-(Pyridin-2-ylmethyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta [c]thien-4-yl)-acetamide (**39**)*

Yield: 40%. M.P. 211 °C. IR (KBr, cm^{-1}): 3372 (NH), 1718 (CO), 1662 (CO amide), 2809, 1508, 1092, 751, 547. ^{1}H-NMR (DMSO d-6) δ (ppm): 8.46 (dd, $^4J_{H6pyridine-H4pyridine}$ = 1.8 Hz, $^3J_{H6pyridine-H5pyridine}$ = 4.9 Hz, 1H, H-$6_{pyridine}$), 8.35 (d, $^3J_{NH-H4c}$ = 8.8 Hz, 1H,NH), 7.74 (dt, $^4J_{H4pyridine-H6pyridine}$ = 1.8 Hz, $^3J_{H4pyridine-H5pyridine}$ = $^3J_{H4pyridine-H3pyridine}$ = 7.7 Hz, 1H, H-$4_{pyridine}$), 7.40 (d, $^3J_{H3pyridine-H4pyridine}$ = 7.7 Hz, 1H, H-$3_{pyridine}$), 7.23 (dd, $^3J_{H5pyridine-H6pyridine}$ = 4.9 Hz, $^3J_{H5pyridine-H4pyridine}$ = 7.7 Hz, 1H, H-$5_{pyridine}$), 5.36 (dt, $^3J_{H4c-H5a}$ = 3.5 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.8 Hz, 1H, H-4c), 3.57 (s, 2H,NC*H_2*pyridine), 3.29 (dd, $^3J_{H5b-H4c}$ = 8.8 Hz, $^2J_{H5b-H5a}$ = 18.7 Hz, 1H, H-5b), 2.92 (s, 2H, COC*H_2*N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.5 Hz, $^2J_{H5a-H5b}$ = 18.7 Hz, 1H, H-5a), 2.55

(m, 8H, $H_{piperazine}$). ^{13}C-NMR (DMSO d-6) δ (ppm): 193.40 (C-6), 168.89 (NHCO), 158.14 (C-$2_{pyridine}$), 153.50 (C-6a), 148.72 (C-$6_{pyridine}$), 142.57 (C-3a), 136.45 (C-$4_{pyridine}$), 122.73 (C-$3_{pyridine}$), 122.11 ($C5_{pyridine}$), 109.50 (C-1), 104.62 (C-3), 63.70 (N*C*H_2 pyridine), 61.26 (CO*C*H_2N), 52.95 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.43 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 51.10 (C-5), 40.12 (C-4). MS (m/z): 530.2 ($^+$M+2), 528.2 ($^+$M), 526.2 ($^+$M–2).

*6.4.39. 2-[4-(Pyridin-3-ylmethyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta [c]thien-4-yl)-acetamide (**40**)*

Yield: 43%. M.P. 241 °C. IR (KBr, cm^{-1}): 3416 (NH), 1718 (CO), 1651 (CO amide), 2807, 1508, 1133, 716, 576. ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.52 (s, 1H, H-$2_{pyridine}$), 8.05 (d, $^3J_{H6pyridine-H5pyridine}$ = 4.7 Hz, 1H H-$6_{pyridine}$), 7.65 (d, $^3J_{H4pyridine-H5pyridine}$ = 7.6 Hz, 1H, H-$4_{pyridine}$), 7.54 (d, $^3J_{NH-H4c}$ = 7.8 Hz, 1H,NH), 7.26 (dd, $^3J_{H5pyridine-H4pyridine}$ = 7.6 Hz, $^3J_{H5pyridine-H6pyridine}$ = 4.7 Hz, 1H, H-$5_{pyridine}$), 5.36 (dt, $^3J_{H4c-H5a}$ = 3.7 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 7.8 Hz, 1H, H-4c), 3.57 (m, 3H, H-5b and N*CH_2*pyridine), 3.06 (s, 2H, CO*CH_2*N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.7 Hz, $^2J_{H5a-H5b}$ = 19.5 Hz, 1H, H-5a), 2.55 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.41 (C-6), 170.18 (NHCO), 151.76 (C-6a), 150.50 (C-$2_{pyridine}$), 148.72 (C-$6_{pyridine}$), 142.57 (C-3a), 136.45 (C-$4_{pyridine}$), 133.39 (C-$3_{pyridine}$), 123.50 ($C5_{pyridine}$), 112.10 (C-1), 106.10 (C-3), 61.40 (CO*C*H_2N), 60.70 (N*C*H_2pyridine), 53.68 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 53.02 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.25 (C-5), 43.16 (C-4). MS (m/z): 530.8 ($^+$M+2), 528.8 ($^+$M), 526.8 ($^+$M–2).

*6.4.40. 2-(4-Pyridin-4-ylmethyl)piperazin-1-yl)-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta [c]thien-4-yl)-acetamide (**41**)*

Yield: 43%. M.P. 241 °C. IR (KBr, cm^{-1}): 3368 (NH), 1717 (CO), 1660 (CO amide), 2820, 1512, 1134, 750, 466. ^{1}H-NMR (DMSO d-6) δ (ppm): 8.48 (d, $^3J_{H2pyridine-H3pyridine}$ = $^3J_{H6pyridine-H5pyridine}$ = 5.3 Hz, 2H, H-$2_{pyridine}$, H-$6_{pyridine}$), 8.34 (d, $^3J_{NH-H4c}$ = 8.7 Hz, 1H,NH), 7.29 (d, $^3J_{H3pyridine-H2pyridine}$ = $^3J_{H5pyridine-H6pyridine}$ = 5.3 Hz, 2H, H-$3_{pyridine}$, H-$5_{pyridine}$), 5.28 (dt, $^3J_{H4c-H5a}$ = 3.5 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.7 Hz, 1H, H-4c), 3.48 (s, 2H,N*CH_2*pyridine), 3.26 (dd, $^3J_{H5b-H4c}$ = 8.7 Hz, $^2J_{H5b-H5a}$ = 18.7 Hz, 1H, H-5b), 2.92 (s, 2H, CO*CH_2*N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.5 Hz, $^2J_{H5a-H5b}$ = 18.7 Hz, 1H, H-5a), 2.55 (m, 8H, $H_{piperazine}$). ^{13}C-NMR (DMSO d-6) δ (ppm): 193.35 (C-6), 168.91 (NHCO), 153.47 (C-6a), 149.48 (C-$2_{pyridine}$ and C-$6_{pyridine}$), 147.31 (C-$4_{pyridine}$), 142.57 (C-3a), 123.75 (C-$3_{pyridine}$ and C-$5_{pyridine}$), 109.58 (C-1), 104.67 (C-3), 61.22 (N*C*H_2pyridine), 60.60 (CO*C*H_2N), 52.91 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.31 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 51.08 (C-5), 42.31 (C-4). MS (m/z): 530.2 ($^+$M+2), 528.2 ($^+$M), 526.2 ($^+$M–2).

*6.4.41. 2-[4-(Thien-2-ylmethyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**42**)*

Yield: 33%. M.P. 170 °C. IR (KBr, cm^{-1}): 3372 (NH), 1718 (CO), 1662 (CO amide), 2811, 1511, 1476, 1130, 1008, 702. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.61 (d, $^3J_{NH-H4c}$ = 8.2 Hz, 1H,NH), 7.23 (dd, $^4J_{H5thiophene-H3thiophene}$ = 1.2 Hz, $^3J_{H5thiophene-H4thiophene}$ = 4.9 Hz, 1H, H-$5_{thiophene}$), 6.94 (dd, $^3J_{H4thiophene-H3thiophene}$ = 3.4 Hz, $^3J_{H4thiophene-H5thiophene}$ = 4.9 Hz, 1H, H-$4_{thiophene}$), 6.89 (dd, $^4J_{H3thiophene-H5thiophene}$ = 1.2 Hz, $^3J_{H3thiophene-H4thiophene}$ = 3.4 Hz, 1H, H-$3_{thiophene}$), 5.35 (dt, $^3J_{H4c-H5a}$ = 3.8 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.2 Hz, 1H, H-4c), 3.71 (s, 2H,N*CH_2*thiophene), 3.47 (dd, $^3J_{H5b-H4c}$ = 8.2 Hz, $^2J_{H5b-H5a}$ = 19.3 Hz, 1H, H-5b), 3.06 (s, 2H, CO*CH_2*N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.8 Hz, $^2J_{H5a-H5b}$ = 19.3 Hz, 1H, H-5a), 2.55 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.30 (C-6), 170.15 (NHCO), 151.73 (C-6a), 141.93 (C-$2_{thiophene}$), 141.16 (C-3a), 126.44 (C-$4_{thiophene}$), 126.09 (C-$5_{thiophene}$), 125.09 (C-$3_{thiophene}$), 111.73 (C-1), 105.94 (C-3), 61.28 (CO*C*H_2N), 56.59 (N*C*H_2thiophene), 53.57 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.58 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.02 (C-5), 43.02 (C-4). MS (m/z): 453.1 ($^+$M+1-Br), 451.1 ($^+$M–1-Br).

*6.4.42. 2-[4-(Thien-3-ylmethyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**43**)*

Yield: 71%. M.P. 203 °C. IR (KBr, cm^{-1}): 3369 (NH), 1716 (CO), 1661 (CO amide), 2811, 1511, 1461, 1130, 1006, 769. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.57 (d, $^3J_{NH-H4c}$ = 8.1 Hz, 1H,NH), 7.27 (dd, $^4J_{H4thiophene-H2thiophene}$ = 3.1 Hz, $^3J_{H4thiophene-H5thiophene}$ = 4.9 Hz, 1H, H-$4_{thiophene}$), 7.10 (d, $^4J_{H2thiophene-H4thiophene}$ = 3.1 Hz, 1H, H-$2_{thiophene}$), 7.04 (d, $^3J_{H5thiophene-H4thiophene}$ = 4.9 Hz, 1H, H-$5_{thiophene}$), 5.36 (dt, $^3J_{H4c-H5a}$ = 3.8 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.1 Hz, 1H, H-4c), 3.54 (s, 2H,N*CH_2*thiophene), 3.49 (dd, $^3J_{H5b-H4c}$ = 8.1 Hz, $^2J_{H5b-H5a}$ = 19.3 Hz, 1H, H-5b), 3.06 (s, 2H, CO*CH_2*N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.8 Hz, $^2J_{H5a-H5b}$ = 19.3 Hz, 1H, H-5a), 2.55 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.33 (C-6), 170.19 (NHCO), 151.69 (C-6a), 141.88 (C-3a), 138.80 (C-$3_{thiophene}$), 128.46 (C-$5_{thiophene}$), 125.54 (C-$4_{thiophene}$), 122.86 (C-$2_{thiophene}$), 111.88 (C-1), 105.98 (C-3), 61.32 (CO*C*H_2N), 57.42 (N*C*H_2thiophene), 53.67 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.12 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.05 (C-5), 42.99 (C-4). HRMS: calculated (530.9287), found (530.9282).

*6.4.43. 2-{4-[(5-Chlorothien-2-yl)methyl]piperazin-1-yl}-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl)acetamide (**44**)*

Yield: 73%. M.P. 188 °C. IR (KBr, cm^{-1}): 3380 (NH), 1719 (CO), 1662 (CO amide), 2813, 1509, 1329, 1129, 1092, 784. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.55 (d, $^3J_{NH-H4c}$ = 8.2 Hz, 1H,NH), 6.73 (d, $^3J_{H4thiophene-H3thiophene}$ = 3.6 Hz, 1H, H-$4_{thiophene}$), 6.65 (d, $^3J_{H3thiophene-H4thiophene}$ = 3.6 Hz, 1H, H-$3_{thiophene}$), 5.37 (dt, $^3J_{H4c-H5a}$ = 3.7 Hz, $^3J_{H4c-H5b}$ =

$^{3}J_{H4c\text{-}NH}$ = 8.2 Hz, 1H, H-4c), 3.61 (s, 2H,NCH_2thiophene), 3.50 (dd, $^{3}J_{H5b\text{-}H4c}$ = 8.2 Hz, $^{2}J_{H5b\text{-}H5a}$ = 19.3 Hz, 1H, H-5b), 3.06 (s, 2H, COCH_2N), 2.82 (dd, $^{3}J_{H5a\text{-}H4c}$ = 3.7 Hz, $^{2}J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.55 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.33 (C-6), 170.10 (NHCO), 151.68 (C-6a), 141.94 (C-$2_{thiophene}$), 140.74 (C-3a), 129.33 (C-$5_{thiophene}$), 125.41 (C-$3_{thiophene}$), 125.00 (C-$4_{thiophene}$), 111.91 (C-1), 105.98 (C-3), 61.25 (COCH_2N), 57.32 (NCH_2thiophene), 53.58 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.61 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.13 (C-5), 43.04 (C-4). MS (m/z): 569.9 ($^{+}$M+2), 567.9 ($^{+}$M), 565.9 ($^{+}$M–2).

*6.4.44. 2-{4-[(2,5-Dimethoxythien-3-yl)methyl]piperazin-1-yl}-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl)acetamide (**45**)*

Yield: 71%. M.P. >240 °C. IR (KBr, cm^{-1}): 3419 (NH), 1716 (CO), 1640 (CO amide), 2926, 1455, 1261, 1233, 1016, 801. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.57 (d, $^{3}J_{NH\text{-}H4c}$ = 8.1 Hz, 1H,NH), 7.27 (s, 1H, H-$4_{thiophene}$), 5.36 (dt, $^{3}J_{H4c\text{-}H5a}$ = 3.8 Hz, $^{3}J_{H4c\text{-}H5b}$ = $^{3}J_{H4c\text{-}NH}$ = 8.1 Hz, 1H, H-4c), 3.74 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.45 (s, 2H,NCH_2thiophene), 3.40 (dd, $^{3}J_{H5b\text{-}H4c}$ = 8.1 Hz, $^{2}J_{H5b\text{-}H5a}$ = 19.7 Hz, 1H, H-5b), 3.06 (s, 2H, COCH_2N), 2.76 (dd, $^{3}J_{H5a\text{-}H4c}$ = 3.8 Hz, $^{2}J_{H5a\text{-}H5b}$ = 19.7 Hz, 1H, H-5a), 2.68 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.43 (C-6), 169.68 (NHCO), 154.59 (C-$5_{thiophene}$), 151.73 (C-6a), 151.42 (C-$2_{thiophene}$), 141.91 (C-3a), 114.07 (C-$3_{thiophene}$), 111.84 (C-1), 106.02 (C-3), 102.90 (C-$4_{thiophene}$), 62.89 (OMe), 61.32 (COCH_2N), 60.16 (OMe), 57.42 (NCH_2thiophene), 53.67 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.12 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.05 (C-5), 42.99 (C-4). HRMS: calculated (590.9495), found (590,9497).

*6.4.45. 2-[4-(Fur-2-ylmethyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**46**)*

Yield: 33%. M.P. 152 °C. IR (KBr, cm^{-1}): 3371 (NH), 1717 (CO), 1662 (CO amide), 817, 1509, 1474, 1262, 1093, 801. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.54 (d, $^{3}J_{NH\text{-}H4c}$ = 8.2 Hz, 1H,NH), 7.38 (d, $^{3}J_{H5furan\text{-}H4furan}$ = 2.2 Hz, 1H, H-5_{furan}), 6.32 (dd, $^{3}J_{H4furan\text{-}H5furan}$ = 2.2 Hz, $^{3}J_{H4furan\text{-}H3furan}$ = 3.0 Hz, 1H, H-4_{furan}), 6.20 (d, $^{3}J_{H3furan\text{-}H4furan}$ = 3.0 Hz, 1H, H-3_{furan}), 5.36 (dt, $^{3}J_{H4c\text{-}H5a}$ = 3.7 Hz, $^{3}J_{H4c\text{-}H5b}$ = $^{3}J_{H4c\text{-}NH}$ = 8.2 Hz, 1H, H-4c), 3.54 (s, 2H,NCH_2furan), 3.50 (dd, $^{3}J_{H5b\text{-}H4c}$ = 8.2 Hz, $^{2}J_{H5b\text{-}H5a}$ = 19.3 Hz, 1H, H-5b), 3.06 (s, 2H, COCH_2N), 2.82 (dd, $^{3}J_{H5a\text{-}H4c}$ = 3.7 Hz, $^{2}J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.55 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.28 (C-6), 170.07 (NHCO), 151.63 (C-6a), 151.19 (C-2_{furan}), 142.26 (C-5_{furan}),141.88 (C-3a), 111.73 (C-1), 110.03 (C-4_{furan}), 108.91 (C-3_{furan}), 105.93 (C-3), 61.21 (COCH_2N), 54.58 (NCH_2furan), 53.41(C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.55 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.04 (C-5), 42.96 (C-4). MS (m/z): 518.7 ($^{+}$M+2), 516.7 ($^{+}$M), 514.7 ($^{+}$M–2).

*6.4.46. 2-[4-(Fur-3-ylmethyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**47**)*

Yield: 21%. M.P. 158 °C. IR (KBr, cm^{-1}): 3371 (NH), 1717 (CO), 1662 (CO amide), 2813, 1508, 1261, 1130, 1020, 801. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.55 (d, $^{3}J_{NH\text{-}H4c}$ = 8.1 Hz, 1H,NH), 7.38 (d, $^{3}J_{H5furan\text{-}H4furan}$ = 1.5 Hz, 1H, H-5_{furan}), 7.33 (s, 1H, H-2_{furan}), 6.38 (d, $^{3}J_{H4furan\text{-}H5furan}$ = 1.5 Hz, 1H, H-4_{furan}), 5.37 (dt, $^{3}J_{H4c\text{-}H5a}$ = 3.7 Hz, $^{3}J_{H4c\text{-}H5b}$ = $^{3}J_{H4c\text{-}NH}$ = 8.1 Hz, 1H, H-4c), 3.49 (dd, $^{3}J_{H5b\text{-}H4c}$ = 8.1 Hz, $^{2}J_{H5b\text{-}H5a}$ = 19.3 Hz, 1H, H-5b), 3.40 (s, 2H,NCH_2furan), 3.06 (s, 2H, COCH_2N), 2.82 (dd, $^{3}J_{H5a\text{-}H4c}$ = 3.7 Hz, $^{2}J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.55 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 191.97 (C-6), 169.79 (NHCO), 151.34 (C-6a), 142.77 (C-5_{furan}), 141.60 (C-3a), 140.58 (C-2_{furan}), 120.64 (C-3_{furan}), 111.55 (C-1), 110.99 (C-4_{furan}), 105.63 (C-3), 60.92 (COCH_2N), 53.15 (NCH_2furan), 52.34 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.33 (C-5), 51.76 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 42.70 (C-4). MS (m/z): 518.7 ($^{+}$M+2), 516.7 ($^{+}$M), 514.7 ($^{+}$M–2).

*6.4.47. 2-[4-(1H-Pyrrol-2-ylmethyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclo-penta[c]thien-4-yl)-acetamide (**48**)*

Yield: 73%. M.P. 209 °C. IR (KBr, cm^{-1}): 3344 (NH), 1720 (CO), 1643 (CO amide), 2820, 1514, 1134, 1002, 835, 725. ^{1}H-NMR ($CDCl_3$) δ (ppm): 9.12 (s, 1H,$NH_{pyrrole}$), 7.46 (d, $^{3}J_{NH\text{-}H4c}$ = 8.2 Hz, 1H,NH_{amide}), 6.72 (dd, $^{4}J_{H5pyrrole\text{-}H3pyrrole}$ = 2.6 Hz, $^{3}J_{H5pyrrole\text{-}H4pyrrole}$ = 4.0 Hz, 1H, H-$5_{pyrrole}$), 6.10 (m, 2H, H-$3_{pyrrole}$ and H-$4_{pyrrole}$), 5.35 (dt, $^{3}J_{H4c\text{-}H5a}$ = 3.7 Hz, $^{3}J_{H4c\text{-}H5b}$ = $^{3}J_{H4c\text{-}NH}$ = 8.2 Hz, 1H, H-4c), 3.71 (s, 2H,NCH_2pyrrole), 3.47 (dd, $^{3}J_{H5b\text{-}H4c}$ = 8.2 Hz, $^{2}J_{H5b\text{-}H5a}$ = 19.3 Hz, 1H, H-5b), 3.06 (s, 2H, COCH_2N), 2.82 (dd, $^{3}J_{H5a\text{-}H4c}$ = 3.7 Hz, $^{2}J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.55 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.16 (C-6), 169.66 (NHCO), 151.85 (C-6a), 142.18 (C-3a), 125.04 (C-$2_{pyrrole}$), 118.98 (C-$5_{pyrrole}$), 112.06 (C-1), 109.39 (C-$4_{pyrrole}$), 108.29 (C-$3_{pyrrole}$), 106.08 (C-3), 61.20 (COCH_2N), 54.92 (NCH_2pyrrole), 52.73 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.37 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.23 (C-5), 43.35 (C-4). MS (m/z): 517.9 ($^{+}$M+2), 515.9 ($^{+}$M), 513.9 ($^{+}$M–2).

*6.4.48. 2-[4-(2-Fluorobenzyl)piperazin-1-yl]-N-(3-bromo-6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl)acetamide (**49**)*

Yield: 57%. M.P. 136 °C. IR (KBr, cm^{-1}): 3329 (NH), 1716 (CO), 1668 (CO amide), 2820, 1506, 1467, 1183, 1133, 726. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.80 (s, 1H, H-1), 7.59 (d, $^{3}J_{NH\text{-}H4c}$ = 8.0 Hz, 1H,NH), 7.36 (dt, $^{4}J_{H6phenyl\text{-}H4phenyl}$ = 1.7 Hz, $^{4}J_{H6phenyl\text{-}F}$ = $^{3}J_{H6phenyl\text{-}H5phenyl}$ = 7.5 Hz, 1H, H-6_{phenyl}), 7.23 (m, 1H, H-4_{phenyl}), 7.11 (dt, $^{4}J_{H5phenyl\text{-}H3phenyl}$ = 1.1 Hz, $^{3}J_{H5phenyl\text{-}H4phenyl}$ = $^{3}J_{H5phenyl\text{-}H6phenyl}$ = 7.5 Hz, 1H, H-5_{phenyl}), 7.02 (dt, $^{4}J_{H3phenyl\text{-}H5phenyl}$ = 1.1 Hz, $^{3}J_{H3phenyl\text{-}H4phenyl}$ = $^{3}J_{H3phenyl\text{-}F}$ = 9.2 Hz, 1H, H-3_{phenyl}), 5.42 (dt, $^{3}J_{H4c\text{-}H5a}$ = 3.9 Hz, $^{3}J_{H4c\text{-}H5b}$ = $^{3}J_{H4c\text{-}NH}$ = 8.0 Hz, 1H, H-4c), 3.58 (s, 2H,

H_{benzyl}), 3.52 (dd, $^3J_{H5b\text{-}H4c}$ = 8.0 Hz, $^2J_{H5b\text{-}H5a}$ = 19.3 Hz, 1H, H-5b), 3.06 (s, 2H, COCH_2N), 2.83 (dd, $^3J_{H5a\text{-}H4c}$ = 3.9 Hz, $^2J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.55 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 193.58 (C-6), 170.28 (NHCO), 161.38 (d, $^1J_{C-F}$ = 245.2 Hz, C-2_{phenyl}), 151.31 (C-6a), 144.36 (C-3a), 131.49 (d, $^3J_{C-F}$ = 4.1 Hz, C-6_{phenyl}), 128.89 (d, $^3J_{C-F}$ = 8.2 Hz, C-4_{phenyl}), 125.76 (C-1), 124.37 (d, $^2J_{C-F}$ = 14.8 Hz, C-1_{phenyl}), 123.92 (d, $^4J_{C-F}$ = 3.3 Hz, C-5_{phenyl}), 115.27 ($^2J_{C-F}$ = 21.4 Hz,C-3_{phenyl}), 106.74 (C-3), 61.37 (COCH_2N), 55.01 (C_{benzyl}), 53.61 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.71 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.11 (C-5), 43.75 (C-4). MS (m/z): 466.9 ($^+$M+1), 464.9 ($^+$M–1).

*6.4.49. 2-[4-(2-Fluorobenzyl)piperazin-1-yl]-N-(6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl) acetamide (**50**)*

Yield: 32%. M.P. 130 °C. IR (KBr, cm^{-1}): 3350 (NH), 1711 (CO), 1662 (CO amide), 2823, 1513, 1455, 1154, 1008, 758. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.85 (s, 1H, H-1), 7.54 (d, $^3J_{NH\text{-}H4c}$ = 7.8 Hz, 1H,NH), 7.34 (t, $^4J_{H6phenyl\text{-}F}$ = $^3J_{H6phenyl\text{-}H5phenyl}$ = 7.1 Hz, 1H, H-6_{phenyl}), 7.27 (s, 1H, H-3), 7.23 (m, 1H, H-4_{phenyl}), 7.11 (t, $^4J_{H5phenyl\text{-}H4phenyl}$ = $^3J_{H5phenyl\text{-}H6phenyl}$ = 7.1 Hz, 1H, H-5_{phenyl}), 7.02 (t, $^3J_{H3phenyl\text{-}H4phenyl}$ = $^3J_{H3phenyl\text{-}F}$ = 9.2 Hz, 1H, H-3_{phenyl}), 5.35 (m, 1H, H-4c), 3.58 (s, 2H, H_{benzyl}), 3.50 (dd, $^3J_{H5b\text{-}H4c}$ = 7.6 Hz, $^2J_{H5b\text{-}H5a}$ = 19.0 Hz, 1H, H-5b), 3.06 (s, 2H, COCH_2N), 2.78 (dd, $^3J_{H5a\text{-}H4c}$ = 3.3 Hz, $^2J_{H5a\text{-}H5b}$ = 19.0 Hz, 1H, H-5a), 2.60 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 194.14 (C-6), 170.16 (NHCO), 161.23 (d, $^1J_{C-F}$, = 246.8 Hz, C-2_{phenyl}), 154.15 (C-6a), 143.71 (C-3a), 131.40 (C-6_{phenyl}), 128.82 (C-4_{phenyl}), 124.64 (C-1), 124.00 (d, $^2J_{C-F}$ = 14.8 Hz, C-1_{phenyl}), 123.79 (C-5_{phenyl}), 119.57 (C-3), 115.12 (d, $^2J_{C-F}$ = 22.2 Hz, C-3_{phenyl}), 61.21 (COCH_2N), 54.84 (C_{benzyl}), 53.36 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.48 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 51.45 (C-5), 43.49 (C-4). MS (m/z): 387.1 ($^+$M).

*6.4.50. 2-[4-(2-Fluorobenzyl)piperazin-1-yl]-N-(1,3-dimethyl-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**51**)*

Yield: 71%. M.P. 153 °C. IR (KBr, cm^{-1}): 3434 (NH), 1705 (CO), 1643 (CO amide), 2817, 1514, 1178, 1015, 838, 768. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.32 (d, $^3J_{NH\text{-}H4c}$ = 8.3 Hz, 1H,NH), 7.27 (t, $^4J_{H6phenyl\text{-}F}$ = $^3J_{H6phenyl\text{-}H5phenyl}$ = 7.3 Hz, 1H, H-6_{phenyl}), 7.15 (m, 1H, H-4_{phenyl}), 7.03 (t, $^3J_{H5phenyl\text{-}H4phenyl}$ = $^3J_{H5phenyl\text{-}H6phenyl}$ = 7.3 Hz, 1H, H-5_{phenyl}), 6.95 (t, $^3J_{H3phenyl\text{-}H4phenyl}$ = $^3J_{H3phenyl\text{-}F}$ = 9.2 Hz, 1H, H-3_{phenyl}), 5.36 (dt, $^3J_{H4c\text{-}H5a}$ = 2.3 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.3 Hz, 1H, H-4c), 3.50 (s, 2H, H_{benzyl}), 3.35 (dd, $^3J_{H5b\text{-}H4c}$ = 8.3 Hz, $^2J_{H5b\text{-}H5a}$ = 19.1 Hz, 1H, H-5b), 2.96 (s, 2H, COCH_2N), 2.64 (dd, $^3J_{H5a\text{-}H4c}$ = 2.3 Hz, $^2J_{H5a\text{-}H5b}$ = 19.1 Hz, 1H, H-5a), 2.45 (m, 14H, $H_{piperazine}$ and C1-Me and C3-Me). ^{13}C-NMR ($CDCl_3$) δ (ppm): 195.58 (C-6), 169.80 (NHCO), 161.40 (d, $^1J_{C-F}$ = 246.1 Hz, C-2_{phenyl}), 147.93(C-6a), 141.14 (C-1), 139.31 (C-3), 131.48 (d, $^3J_{C-F}$ = 5.1 Hz, C-6_{phenyl}), 130.28 (C-3a), 128.89 (d, $^3J_{C-F}$ = 8.2 Hz, C-4_{phenyl}), 124.37 (d, $^2J_{C-F}$ = 14.9 Hz, C-1_{phenyl}), 123.91 (d, $^4J_{C-F}$ = 3.3 Hz, C-5_{phenyl}), 115.25 (d, $^2J_{C-F}$ = 22.4 Hz, C-3_{phenyl}), 61.44 (COCH_2N), 55.00 (C_{benzyl}), 53.60 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.65 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.51 (C-5), 42.48 (C-4), 13.389 (C1-Me), 12.48 (C3-Me). MS (m/z): 415.7 ($^+$M).

*6.4.51. 2-[4-(2-Fluorobenzyl)piperazin-1-yl]-N-(6-oxo-5,6-dihydro-4H-cyclopenta[b]thien-4-yl) acetamide (**52**)*

Yield: 28%. M.P. 130 °C. IR (KBr, cm^{-1}): 3446 (NH), 1700 (CO), 1660 (CO amide), 2820, 1507, 1455, 1129, 1095, 760. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.85 (d, $^3J_{H2\text{-}H3}$ = 4.6 Hz, 1H, H-2), 7.43 (d, $^3J_{NH\text{-}H4c}$ = 7.6 Hz, 1H,NH), 7.27 (dt, $^4J_{H6phenyl\text{-}H4phenyl}$ = 1.7 Hz, $^4J_{H6phenyl\text{-}F}$ = $^3J_{H6phenyl\text{-}H5phenyl}$ = 7.0 Hz, 1H, H-6_{phenyl}), 7.16 (m, 1H, H-4_{phenyl}), 7.02 (m, 2H, H-$5_{phenyl}$and H-3), 6.93 (dt, $^4J_{H3phenyl\text{-}H5phenyl}$ = 1.0 Hz, $^3J_{H3phenyl\text{-}H4phenyl}$ = $^3J_{H3phenyl\text{-}F}$ = 9.2 Hz, 1H, H-3_{phenyl}), 5.51 (dt, $^3J_{H4c\text{-}H5a}$ = 2.5 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 7.6 Hz, 1H, H-4c), 3.49 (s, 2H, H_{benzyl}), 3.37 (dd, $^3J_{H5b\text{-}H4c}$ = 7.6 Hz, $^2J_{H5b\text{-}H5a}$ = 18.6 Hz, 1H, H-5b), 2.98 (s, 2H, COCH_2N), 2.67 (dd, $^3J_{H5a\text{-}H4c}$ = 2.5 Hz, $^2J_{H5a\text{-}H5b}$ = 18.6 Hz, 1H, H-5a), 2.45 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 193.15 (C-6), 170.10 (NHCO), 167.24 (C-3a), 161.18 (d, $^1J_{C-F}$ = 244.4 Hz, C-2_{phenyl}), 141.82 (C-6a), 141.25 (C-2), 131.37 (d, $^3J_{C-F}$ = 5.0 Hz, C-6_{phenyl}), 128.77 (d, $^3J_{C-F}$ = 8.2 Hz, C-4_{phenyl}), 124.00 (d, $^2J_{C-F}$ = 14.9 Hz, C-1_{phenyl}), 123.75 (d, $^4J_{C-F}$ = 3.3 Hz, C-5_{phenyl}), 123.20 (C-3), 115.08 (d, $^2J_{C-F}$ = 22.2 Hz, C-3_{phenyl}), 61.18 (COCH_2N), 54.78 (C_{benzyl}), 53.28 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.38 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 49.21 (C-5), 44.58 (C-4). MS (m/z): 387.3 ($^+$M).

*6.4.52. 2-[4-(2-Fluorobenzyl)piperazin-1-yl]-N-(2-bromo-4-oxo-5,6-dihydro-4H-cyclopenta[b]thien-6-yl)acetamide (**53**)*

Yield: 50%. M.P. 155 °C. IR (KBr, cm^{-1}): 3439 (NH), 1707 (CO), 1663 (CO amide), 2813, 1505, 1390, 1155, 1010, 755. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.53 (d, $^3J_{NH\text{-}H6c}$ = 7.0 Hz, 1H,NH), 7.24 (t, $^4J_{H6phenyl\text{-}F}$ = $^3J_{H6phenyl\text{-}H5phenyl}$ = 7.3 Hz, 1H, H-6_{phenyl}), 7.16 (m, 1H, H-4_{phenyl}), 7.00 (m, 2H, H-$5_{phenyl}$and H-3), 6.92 (t, $^3J_{H3phenyl\text{-}H4phenyl}$ = $^3J_{H3phenyl\text{-}F}$ = 9.2 Hz, 1H, H-3_{phenyl}), 5.42 (dt, $^3J_{H6c\text{-}H5a}$ = 2.5 Hz, $^3J_{H6c\text{-}H5b}$ = $^3J_{H6c\text{-}NH}$ = 7.0 Hz, 1H, H-6c), 3.49 (s, 2H, H_{benzyl}), 3.24 (dd, $^3J_{H5b\text{-}H6c}$ = 7.0 Hz, $^2J_{H5b\text{-}H5a}$ = 18.3 Hz, 1H, H-5b), 2.96 (s, 2H, COCH_2N), 2.58 (dd, $^3J_{H5a\text{-}H6c}$ = 2.5 Hz, $^2J_{H5a\text{-}H5b}$ = 18.3 Hz, 1H, H-5a), 2.45 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.79 (C-6), 170.78 (NHCO), 168.59 (C-6a), 161.12 (d, $^1J_{C-F}$ = 246.2 Hz, C-2_{phenyl}), 144.93 (C-3a), 131.28 (d, $^3J_{C-F}$ = 4.9 Hz, C-6_{phenyl}), 128.67 (d, $^3J_{C-F}$ = 8.3 Hz, C-4_{phenyl}), 124.04 (d, $^2J_{C-F}$ = 14.9 Hz, C-1_{phenyl}), 123.64 (d, $^4J_{C-F}$ = 3.3 Hz, C-5_{phenyl}), 121.33 (C-3), 119.81 (C-2), 115.02 (d, $^2J_{C-F}$ = 22.3 Hz, C-3_{phenyl}), 60.96 (COCH_2N), 54.75 (C_{benzyl}), 53.31 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.37 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 46.85 (C-5), 46.04 (C-4). MS (m/z): 467.0 ($^+$M+1), 465.0 ($^+$M–1).

*6.4.53. 2-[4-(2-Fluorobenzyl)piperazin-1-yl]-N-(2,3-dibromo-4-oxo-5,6-dihydro-4H-cyclopenta[b] thien-4-yl)-acetamide (**54**)*

Yield: 58%. M.P. 85 °C. IR (KBr, cm^{-1}): 3340 (NH), 1716 (CO), 1661 (CO amide), 2931, 1492, 1456, 1261, 1106, 759. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.47 (d, $^3J_{NH-H6c}$ = 7.2 Hz, 1H,NH), 7.27 (t, $^4J_{H6phenyl-F}$ = $^3J_{H6phenyl-H5phenyl}$ = 7.3 Hz, 1H, H-6_{phenyl}), 7.05 (m, 3H, H-3_{phenyl}, H-4_{phenyl} and H-5_{phenyl}), 5.61 (m, 1H, H-6c), 3.53 (s, 2H, H_{benzyl}), 3.33 (dd, $^3J_{Hb-H6c}$ = 7.0 Hz, $^2J_{H5b-H5a}$ = 18.4 Hz, 1H, H-5b), 2.99 (s, 2H, COCH_2N), 2.65 (dd, $^3J_{H5a-H6c}$ = 2.6 Hz, $^2J_{H5a-H5b}$ = 18.4 Hz, 1H, H-5a), 2.47 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 191.28 (C-4), 171.39 (NHCO), 168.16 (C-6a), 161.40 (d, $^1J_{C–F}$ = 245.1 Hz, C-2_{phenyl}), 141.69 (C-3a), 131.57 (d, $^3J_{C–F}$ = 4.1 Hz, C-6_{phenyl}), 128.98 (d, $^3J_{C–F}$ = 7.4 Hz, C-4_{phenyl}), 123.91 (m, 2C, C-1_{phenyl} and C-5_{phenyl}), 118.98 (C-2), 115.31 (d, $^2J_{C–F}$ = 21.4 Hz, C-3_{phenyl}), 107.52 (C-3), 61.06 (COCH_2N), 55.00 (C_{benzyl}), 53.54 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.59 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 47.25 (C-5), 45.75 (C-6). MS (m/z): 547.7 ($^+$M+2), 545.7 ($^+$M), 543.7 ($^+$M–2).

*6.4.54. 2-[4-(2-Fluorobenzyl)piperazin-1-yl]-N-(1,3-dichloro-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**55**)*

Yield: 77%. M.P. 220 °C. IR (KBr, cm^{-1}): 3366 (NH), 1722 (CO), 1657 (CO amide), 2815, 1491, 1230, 1140, 752. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.57 (d, $^3J_{NH-H4c}$ = 8.0 Hz, 1H,NH), 7.35 (dt, $^4J_{H6phenyl-H4phenyl}$ = 1.7 Hz, $^4J_{H6phenyl-F}$ = $^3J_{H6phenyl-H5phenyl}$ = 7.4 Hz, 1H, H-6_{phenyl}), 7.24 (m, 1H, H-4_{phenyl}), 7.11 (dt, $^4J_{H5phenyl-H3phenyl}$ = 1.0 Hz, $^3J_{H5phenyl-H4phenyl}$ = $^3J_{H5phenyl-H6phenyl}$ = 7.4 Hz, 1H, H-5_{phenyl}), 7.03 (dt, $^4J_{H3phenyl-H5phenyl}$ = 1.0 Hz, $^3J_{H3phenyl-H4phenyl}$ = $^3J_{H3phenyl-F}$ = 9.2 Hz, 1H, H-3_{phenyl}), 5.42 (dt, $^3J_{H4c-H5a}$ = 3.9 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.1 Hz, 1H, H-4c), 3.59 (s, 2H, H_{benzyl}), 3.47 (dd, $^3J_{H5b-H4c}$ = 8.1 Hz, $^2J_{H5b-H5a}$ = 19.3 Hz, 1H, H-5b), 3.05 (s, 2H, COCH_2N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.9 Hz, $^2J_{H5a-H5b}$ = 19.3 Hz, 1H, H-5a), 2.55 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 191.87 (C-6), 170.19 (NHCO), 161.45 (d, $^1J_{C–F}$ = 245.2 Hz, C-2_{phenyl}), 147.45 (C-6a), 138.59 (C-3a), 131.51 (d, $^3J_{C–F}$ = 4.9 Hz, C-6_{phenyl}), 128.82 (d, $^3J_{C–F}$ = 8.2 Hz, C-4_{phenyl}), 127.16 (C-1), 124.37 (d, $^2J_{C–F}$ = 14.8 Hz, C-1_{phenyl}), 123.92 (d, $^4J_{C–F}$ = 3.3 Hz, C-5_{phenyl}), 120.73 (C-3), 115.30 (d, $^2J_{C–F}$ = 22.2 Hz, C-3_{phenyl}), 61.31 (COCH_2N), 55.03 (C_{benzyl}), 53.60 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.70 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 51.92 (C-5), 42.84 (C-4). MS (m/z): 455.0 ($^+$M+2), 457.0 ($^+$M), 459.0 ($^+$M–2).

*6.4.55. 2-[4-(Cyclohexylmethyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta [c]thien-4-yl)-acetamide (**56**)*

Yield: 30%. M.P. 177 °C. IR (KBr, cm^{-1}): 3377 (NH), 1720 (CO), 1662 (CO amide), 2922, 1509, 1128, 1014, 590. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.55 (d, $^3J_{NH-H4c}$ = 8.1 Hz, 1H,NH), 5.37 (dt, $^3J_{H4c-H5a}$ = 3.6 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.0 Hz, 1H, H-4c), 3.43 (dd, $^3J_{H5b-H4c}$ = 8.0 Hz, $^2J_{H5b-H4c}$ = 19.3 Hz, 1H, H-5b), 2.98 (s, 2H, COCH_2N), 2.82 (dd, $^3J_{H5a-H4c}$ = 3.6 Hz, $^2J_{H5a-H5b}$ = 19.3 Hz, 1H, H-5a), 2.48 (m, 8H, $H_{piperazine}$), 2.06 (m, 2H,NCH_2CH), 1.65 (m, 6H, H-$3_{cyclohexyl}$, H-$4_{cyclohexyl}$ and H-$5_{cyclohexyl}$), 1.39 (m, 1H, H-$1_{cyclohexyl}$), 1.15 (m, 4H, H-$2_{cyclohexyl}$ and H-$6_{cyclohexyl}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.38 (C-6), 170.26 (NHCO), 151.63 (C-6a), 141.88 (C-3a), 111.83 (C-1), 105.94 (C-3), 65.39 (NCH$_2$CH), 61.29 (COCH_2N), 53.60 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 53.50 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.08 (C-5), 42.97 (C-4), 34.89 (C-$1_{cyclohexyl}$), 31.78 (C-$2_{cyclohexyl}$ and C-$6_{cyclohexyl}$), 26.70 (C-$4_{cyclohexyl}$), 26.05 (C-$3_{cyclohexyl}$ and C-$5_{cyclohexyl}$). MS (m/z): 535.6 ($^+$M+2), 533.6 ($^+$M), 531.6 ($^+$M–2).

*6.4.56. 2-(4-Phenylpiperazin-1-yl)-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl) acetamide (**57**)*

Yield: 46%. M.P. 205 °C. IR (KBr, cm^{-1}): 3438 (NH), 1712 (CO), 1663 (CO amide), 2824, 1503, 1471, 1239, 758. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.59 (d, $^3J_{NH-H4c}$ = 8.1 Hz, 1H,NH), 7.26 (t, $^3J_{H3phenyl-H2phenyl}$ = $^3J_{H3phenyl-H4phenyl}$ = $^3J_{H5phenyl-H4phenyl}$ = $^3J_{H5phenyl-H6phenyl}$ = 8.1 Hz, 2H, H-3_{phenyl} and H-5_{phenyl}), 6.89 (m, 3H, H-2_{phenyl}, H-4_{phenyl} and H-6_{phenyl}), 5.36 (dt, $^3J_{H4c-H5a}$ = 3.7 Hz, $^3J_{H4c-H5b}$ = $^3J_{H4c-NH}$ = 8.1 Hz, 1H, H-4c), 3.53 (dd, $^3J_{H5b-H4c}$ = 8.1 Hz, $^2J_{H5b-H5a}$ = 19.3 Hz, 1H, H-5b), 3.18 (m, 6H, , COCH_2N, $H_{piperazine}$-3 and $H_{piperazine}$-5), 2.84 (dd, $^3J_{H5a-H4c}$ = 3.7 Hz, $^2J_{H5a-H5b}$ = 19.3 Hz, 1H, H-5a), 2.71 (m, 4H, $H_{piperazine}$-2 and $H_{piperazine}$-6). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.23 (C-6), 169.96 (NHCO), 151.66 (C-6a), 150.97 (C-1_{phenyl}), 141.98 (C-3a), 129.18 (C-3_{phenyl} and C-5_{phenyl}), 120.14 (C-4_{phenyl}), 116.23 (C-2_{phenyl} and C-6_{phenyl}), 112.012 (C-1), 105.94 (C-3), 61.42 (COCH_2N), 53.68 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.17 (C-5), 49.29 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 43.19 (C-4).). MS (m/z): 515.6 ($^+$M+2), 513.6 ($^+$M), 511.6 ($^+$M–2).

*6.4.57. 2-[4-(2-Phenylethyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-acetamide (**58**)*

Yield: 50%. M.P. 198 °C. IR (KBr, cm^{-1}): 3364 (NH), 1716 (CO), 1660 (CO amide), 2811, 1514, 1130, 1007, 697. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.54 (d, $^3J_{NH-H4c}$ = 6.5 Hz, 1H,NH), 7.28 (m, 5H, H_{phenyl}), 5.36 (m, 1H, H-4c), 3.51 (dd, $^3J_{H5b-H4c}$ = 6.7 Hz, $^2J_{H5b-H4c}$ = 18.1 Hz, 1H, H-5b), 3.00 (s, 2H, COCH_2N), 2.62 (m, 13H, H-5a, NCH_2CH_2Ph and 8$H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.33 (C-6), 170.07 (NHCO), 151.69 (C-6a), 141.92 (C-3a), 139.96 (C-1_{phenyl}), 128.62 (C-2_{phenyl} and C-6_{phenyl}), 128.39 (C-3_{phenyl} and C-5_{phenyl}), 126.11 (C-4_{phenyl}), 111.82 (C-1), 105.96 (C-3), 61.30 (COCH_2N), 60.18 (CH$_2$Ph), 53.53 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 53.03 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.01 (C-5), 43.01 (C-4), 33.48 (CH$_2$CH$_2$Ph). MS (m/z): 544.0 ($^+$M+2), 542.0 ($^+$M), 540.0 ($^+$M–2).

*6.4.58. 2-(4-Benzyl-1,4-Diazepan-1-yl)-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl)acetamide (**62**)*

Yield: 76%. M.P. 209 °C. IR (KBr, cm^{-1}): 3427 (NH), 1717 (CO), 1660 (CO amide), 2809, 1501, 1467, 1131, 753. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.81 (d, $^{3}J_{NH-H4c}$ = 8.3 Hz, 1H,NH), 7.23-715 (m, 5H, H_{phenyl}), 5.31 (dt, $^{3}J_{H4c-H5a}$ = 3.8 Hz, $^{3}J_{H4c-H5b}$ = $^{3}J_{H4c-NH}$ = 8.3 Hz, 1H, H-4c), 3.57 (s, 2H, H_{benzyl}), 3.37 (dd, $^{3}J_{H5b-H4c}$ = 8.3 Hz, $^{2}J_{H5b-H5a}$ = 19.3 Hz, 1H, H-5b), 3.13 (s, 2H, COCH_2N), 2.68 (m, 9H, H-5a, H-$2_{diazepane}$, H-$3_{diazepane}$, H-$5_{diazepane}$, H-$7_{diazepane}$), 1.71 (quintet, $^{3}J_{H6-H5}$ = $^{3}J_{H6-H7}$ = 6.0 Hz, 2H, H-$6_{diazepane}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.23 (C-6), 170.74 (NHCO), 151.82 (C-6a), 141.77 (C-3a), 138.20 (C-1_{phenyl}), 128.72 (C-3_{phenyl} and C-5_{phenyl}), 128.13 (C-2_{phenyl} and C-6_{phenyl}), 127.04 (C-4_{phenyl}), 111.38 (C-1), 105.74 (C-3), 62.65 (C_{benzyl}), 61.25 (COCH_2N), 55.87 (C-$3_{diazepane}$), 54.95 (C-$5_{diazepane}$), 54.54 (C-$2_{diazepane}$), 54.03 (C-$7_{diazepane}$), 51.77 (C-5), 42.75 (C-4), 27.69 (C-$6_{diazepane}$). MS (m/z): 542.4 ($^{+}$M+2), 540.4 ($^{+}$M), 540.4 ($^{+}$M–2).

*6.4.59. 2-(4-Benzylpiperidin-1-yl)-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl) acetamide (**63**)*

Yield: 100%. M.P. 230 °C. IR (KBr, cm^{-1}): 3426 (NH), 1716 (CO), 1659 (CO amide), 2922, 1511, 1330, 1128, 699. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.65 (d, $^{3}J_{NH-H4c}$ = 7.3 Hz, 1H,NH), 7.28 (t, $^{3}J_{H3phenyl-H2phenyl}$ = $^{3}J_{H3phenyl-H4phenyl}$ = $^{3}J_{H5phenyl-H4phenyl}$ = $^{3}J_{H5phenyl-H6phenyl}$ = 7.1 Hz, 2H, H-3_{phenyl} and H-5_{phenyl}), 7.19 (t, $^{3}J_{H4phenyl-H3phenyl}$ = $^{3}J_{H4phenyl-H5phenyl}$ = 7.1 Hz, 1H, H-4_{phenyl}), 7.12 (d, $^{3}J_{H2phenyl-H3phenyl}$ = $^{3}J_{H6phenyl-H5phenyl}$ = 7.1 Hz, 2H, H-2_{phenyl} and H-6_{phenyl}), 5.36 (m, 1H, H-4c), 3.51 (dd, $^{3}J_{H5b-H4c}$ = 8.3 Hz, $^{2}J_{H5b-H5a}$ = 19.0 Hz, 1H, H-5b), 3.00 (s, 2H, COCH_2N), 2.05 (m, 13H, H-5a, H_{benzyl} and $H_{piperidine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 191.99 (C-6), 171.00 (NHCO), 151.24 (C-6a), 141.47 (C-3a), 139.79 (C-1_{phenyl}), 128.59 (C-3_{phenyl} and C-5_{phenyl}), 127.78 (C-2_{phenyl} and C-6_{phenyl}), 125.48 (C-4_{phenyl}), 111.37 (C-1), 105.57 (C-3), 61.24 (COCH_2N), 54.00 (C-$2_{piperidine}$ and C-$6_{piperidine}$), 51.66 (C-5), 43.04 (C_{benzyl}), 42.53 (C-4), 36.66 (C-$4_{piperidine}$), 31.74 (C-$3_{piperidine}$ and C-$5_{piperidine}$). MS (m/z): 528.0 ($^{+}$M+2), 526.0 ($^{+}$M), 524.0 ($^{+}$M–2).

*6.4.60. 2-[4-(2-Chlorobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-butanamide (**64**)*

Yield: 77%. M.P. 203 °C. IR (KBr, cm^{-1}): 3300 (NH), 1722 (CO), 1650 (CO amide), 2935, 1471, 1259, 1129, 912, 742. ^{1}H-NMR (DMSO d-6) δ (ppm): 8.55 (d, $^{3}J_{NH-H4c}$ = 8.3 Hz, 1H,NH), 7.32 (dd, $^{4}J_{H3phenyl-H5phenyl}$ = 1.9 Hz, $^{3}J_{H3phenyl-H4phenyl}$ = 7.4 Hz, 1H, H-3_{phenyl}), 7.24 (dd, $^{4}J_{H6phenyl-H4phenyl}$ = 1.7 Hz, $^{3}J_{H6phenyl-H5phenyl}$ = 7.4 Hz, 1H, H-6_{phenyl}), 7.15 (dt, $^{4}J_{H4phenyl-H6phenyl}$ = 1.7 Hz, $^{3}J_{H4phenyl-H3phenyl}$ = $^{3}J_{H4phenyl-H5phenyl}$ = 7.4 Hz, 1H, H-4_{phenyl}), 7.10 (dt, $^{4}J_{H5phenyl-H3phenyl}$ = 1.9 Hz, $^{3}J_{H5phenyl-H4phenyl}$ = $^{3}J_{H5phenyl-H6phenyl}$ = 7.4 Hz, 1H, H-5_{phenyl}), 5.36 (dt, $^{3}J_{H4c-H5a}$ = 3.7 Hz, $^{3}J_{H4c-H5b}$ = $^{3}J_{H4c-NH}$ = 8.3 Hz, 1H, H-4c), 3.42 (m, 3H, H-5b H_{benzyl}), 2.35 (dd, $^{3}J_{H5a-H4c}$ = 3.7 Hz, $^{2}J_{H5a-H5b}$ = 19.4 Hz, 1H, H-5a), 2.45 (m, 14H, $COCH_2CH_2CH_2N$ and $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 192.64 (C-6), 172.60 (NHCO), 152.33 (C-6a), 141.99 (C-3a), 135.45 (C-1_{phenyl}), 134.38 (C-2_{phenyl}), 130.71 (C-6_{phenyl}), 129.46 (C-3_{phenyl}), 128.23 (C-4_{phenyl}), 126.52 (C-5_{phenyl}), 111.64 (C-1), 106.11 (C-3), 59.13 (C_{benzyl}), 58.40 ($CH_2CH_2CH_2N$), 53.14 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.52 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 52.36 (C-5), 43.03 (C-4), 35.87 ($CH_2CH_2CH_2N$), 21.52 ($CH_2CH_2CH_2N$). MS (m/z): 591.6 ($^{+}$M+2), 589.6 ($^{+}$M), 587.6 ($^{+}$M–2).

*6.5. General experimental procedure for the synthesis of **59–61***

To a solution of one of the compounds **13**, **20** or **43** (1 mmol) in ethanol (10 ml) was added a solution of hydroxylamine hydrochloride (256 mg, 4 mmol) and sodium acetate (328 mg, 4 mmol) in water (3 ml). The reaction mixture was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue was diluted with methylene chloride (50 ml) and washed several times with water. The organic layer was dried over $MgSO_4$, and evaporated under reduced pressure. The product was purified by flash chromatography.

*6.5.1. 2-[4-(2-Chlorobenzyl)piperazin-1-yl]-N-[(6E)-1,3-dibromo-6-(hydroximino)-5,6-dihydro-4H-cyclopenta[c]thien-4-yl]acetamide (**59**)*

Yield: 75%. M.P. >240 °C. IR (KBr, cm^{-1}): 3372 (NH), 2819 (OH), 1672 (CO), 1499, 1444, 1264, 1163, 1011, 754. ^{1}H-NMR (DMSO-d6) δ (ppm): 11.46 (s, 1H, OH), 8.37 (d, $^{3}J_{NH-H4c}$ = 8.7 Hz, 1H,NH), 7.52 (dd, $^{4}J_{H3phenyl-H5phenyl}$ = 1.5 Hz, $^{3}J_{H3phenyl-H4phenyl}$ = 7.3 Hz, 1H, H-3_{phenyl}), 7.46 (dd, $^{4}J_{H6phenyl-H4phenyl}$ = 1.0 Hz, $^{3}J_{H6phenyl-H5phenyl}$ = 7.3 Hz, 1H, H-6_{phenyl}), 7.37 (dt, $^{4}JH_{4phenyl-H6phenyl}$ = 1.0 Hz, $^{3}J_{H4phenyl-H3phenyl}$ = $^{3}J_{H4phenyl-H5phenyl}$ = 7.3 Hz, 1H, H-4_{phenyl}), 7.32 (dt, $^{4}J_{H5phenyl-H3phenyl}$ = 1.5 Hz, $^{3}J_{H5phenyl-H4phenyl}$ = $^{3}J_{H5phenyl-H6phenyl}$ = 7.3 Hz, 1H, H-5_{phenyl}), 5.25 (dt, $^{3}J_{H4c-H5a}$ = 4.1 Hz, $^{3}J_{H4c-H5b}$ = $^{3}J_{H4c-NH}$ = 8.7 Hz, 1H, H-4c), 3.60 (s, 2H, H_{benzyl}), 3.55 (dd, $^{3}J_{H5b-H4c}$ = 8.7 Hz, $^{2}J_{H5b-H5a}$ = 18.8 Hz, 1H, H-5b), 2.98 (s, 2H, COCH_2N), 2.89 (dd, $^{3}J_{H5a-H4c}$ = 4.1 Hz, $^{2}J_{H5a-H5b}$ = 18.8 Hz, 1H, H-5a), 2.55 (m, 8H, $H_{piperazine}$). ^{13}C-NMR (DMSO-d6) δ (ppm): 169.16 (NHCO), 152.84 (C-6), 150.69 (C-6a), 141.69 (C-3a), 136.00 (C-1_{phenyl}), 133.71 (C-2_{phenyl}), 131.31 (C-6_{phenyl}), 129.68 (C-3_{phenyl}), 129.03 (C-4_{phenyl}), 127.47 (C-5_{phenyl}), 104.19 (C-1), 101.76 (C-3), 61.64 (COCH_2N), 58.97 (C_{benzyl}), 53.36 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.87 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 45.02 (C-5), 41.01 (C-4). MS (m/z): 578.5 ($^{+}$M+2), 576.5 ($^{+}$M), 574.5 ($^{+}$M–2).

*6.5.2. 2-[4-(2-Fluororobenzyl)piperazin-1-yl]-N-[(6E)-1,3-dibromo-6-(hydroxyimino)-5,6-dihydro-4H-cyclopenta[c]thien-4-yl]acetamide (**60**)*

Yield: 75%. M.P. 150 °C. IR (KBr, cm-1): 3346 (NH), 2820 (OH), 1652 (CO), 1517, 1455, 1226, 1131, 1007, 758.

1H-NMR ($CDCl_3$) δ (ppm): 10.76 (s, 1H, OH), 7.56 (d, $^3J_{NH\text{-}H4c}$ = 8.6 Hz, 1H,NH), 7.36 (dt, $^4J_{H6phenyl\text{-}H4phenyl}$ = 1.7 Hz, $^4J_{H6phenyl\text{-}F}$ = $^3J_{H6phenyl\text{-}H5phenyl}$ = 7.5 Hz, 1H, H-6_{phenyl}), 7.22 (m, 1H, H-4_{phenyl}), 7.10 (dt, $^4J_{H5phenyl\text{-}H3phenyl}$ = 1.1 Hz, $^3J_{H5phenyl\text{-}H4phenyl}$ = $^3J_{H5phenyl\text{-}H6phenyl}$ = 7.5 Hz, 1H, H-5_{phenyl}), 7.02 (ddd, $^4J_{H3phenyl\text{-}H5phenyl}$ = 1.1 Hz, $^3J_{H3phenyl\text{-}H4phenyl}$ = 8.5 Hz, $^3J_{H3phenyl\text{-}F}$ = 9.8 Hz, 1H, H-3_{phenyl}), 5.38 (dt, $^3J_{H4c\text{-}H5a}$ = 3.6 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.6 Hz, 1H, H-4c), 3.72 (dd, $^3J_{H5b\text{-}H4c}$ = 8.6 Hz, $^2J_{H5b\text{-}H5a}$ = 19.3 Hz, 1H, H-5b), 3.60 (s, 2H, H_{benzyl}), 3.07 (s, 2H, $COCH_2N$), 2.95 (dd, $^3J_{H5a\text{-}H4c}$ = 3.6 Hz, $^2J_{H5a\text{-}H5b}$ = 19.3 Hz, 1H, H-5a), 2.60 (m, 8H, $H_{piperazine}$). ^{13}C-NMR (DMSO-d6) δ (ppm): 168.74 (NHCO), 161.41 (d, $^1J_{C\text{–}F}$ = 246.2 Hz, C-2_{phenyl}), 153.35 (C-6), 148.49 (C-6a), 139.89 (C-3a), 131.68 (d, $^3J_{C\text{–}F}$ = 4.1 Hz, C-6_{phenyl}), 129.09 (d, $^3J_{C\text{–}F}$ = 7.4 Hz, C-4_{phenyl}), 124.11 (d, $^2J_{C\text{–}F}$ = 14.8 Hz, C-1_{phenyl}), 123.97 (d, $^4J_{C\text{–}F}$ = 3.3 Hz, C-5_{phenyl}), 115.42 ($^2J_{C\text{–}F}$ = 22.3 Hz, C-3_{phenyl}), 106.04 (C-1), 103.59 (C-3), 62.12 ($COCH_2N$), 54.88 (C_{benzyl}), 53.54 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.17 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 44.93 (C-5), 41.42 (C-4). HRMS: calculated (557.9734), found (557,9822).

6.5.3. 2-[4-(Thien-3-ylmethyl)piperazin-1-yl]-N-[(6E)-1,3-dibromo-6-(hydroxyimino)-5,6-dihydro-4H-cyclopenta[c]thien-4-yl]acetamide (*61*)

Yield: 70%. M.P. 185 °C. IR (KBr, cm^{-1}): 3305 (NH), 2820 (OH), 1661 (CO), 1506, 1456, 1261, 1130, 1008, 834. ^{1}H-NMR ($CDCl_3$) δ (ppm): 10.66 (s, 1H, OH), 7.57 (d, $^3J_{NH\text{-}H4c}$ = 8.8 Hz, 1H,NH), 7.20 (dd, $^4J_{H4thiophene\text{-}H2thiophene}$ = 2.9 Hz, $^3J_{H4thiophene\text{-}H5thiophene}$ = 4.9 Hz, 1H, H-$4_{thiophene}$), 7.06 (d, $^4J_{H2thiophene\text{-}H4thiophene}$ = 2.9 Hz, 1H, H-$2_{thiophene}$), 7.04 (d, $^3J_{H5thiophene\text{-}H4thiophene}$ = 4.9 Hz, 1H, H-$5_{thiophene}$), 5.31 (dt, $^3J_{H4c\text{-}H5a}$ = 3.2 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.8 Hz, 1H, H-4c), 3.62 (dd, $^3J_{H5b\text{-}H4c}$ = 8.8 Hz, $^2J_{H5b\text{-}H5a}$ = 18.8 Hz, 1H, H-5b), 3.49 (s, 2H,NCH_2thiophene), 3.05 (s, 2H, $COCH_2N$), 2.87 (dd, $^3J_{H5a\text{-}H4c}$ = 3.2 Hz, $^2J_{H5a\text{-}H5b}$ = 18.8 Hz, 1H, H-5a), 2.58 (m, 8H, $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 168.75 (NHCO), 153.28 (C-6), 148.49 (C-6a), 139.94 (C-3a), 138.30 (C-$3_{thiophene}$), 128.53 (C-$5_{thiophene}$), 125.61 (C-$4_{thiophene}$), 123.24 (C-$2_{thiophene}$), 106.03 (C-1), 103.51 (C-3), 62.11 ($COCH_2N$), 57.26 (NCH_2thiophene), 53.55 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 52.38 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 44.92 (C-5), 41.43 (C-4). MS (m/z): 549.7 ($^+$M+2), 547.7 ($^+$M), 545.7 ($^+$M–2).

6.5.4. 2-[4-(2-Chlorobenzyl)piperazin-1-yl]-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c] thien-4-yl)-propanamide (*65*)

To a solution of **94** (1.5 mmol) in acetonitrile (10 ml) was added 1-(2-chlorobenzyl)-piperazine (3 mmol). The reaction mixture was refluxed for 4 h. The solvent was then removed under reduced pressure to give an oil which was dissolved in methylene chloride and washed several times with water. The combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure and the product was purified by flash chromatography. Yield: 43%. M.P. 152 °C. IR (KBr, cm^{-1}): 3421 (NH), 1714 (CO), 1670 (CO amide), 2926, 1508, 1446, 1090, 804. ^{1}H-NMR ($CDCl_3$) δ (ppm): 9.36 (d, $^3J_{NH\text{-}H4c}$ = 8.0 Hz, 1H,NH), 7.46-7.17 (m, 4H, H_{phenyl}), 5.12 (dt, $^3J_{H4c\text{-}H5a}$ = 3.0 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.0 Hz, 1H, H-4c), 3.42 (s, 2H, H_{benzyl}), 3.37 (dd, $^3J_{H5b\text{-}H4c}$ = 8.0 Hz, $^2J_{H5b\text{-}H5a}$ = 18.6 Hz, 1H, H-5b), 2.72 (dd, $^3J_{H5a\text{-}H4c}$ = 3.0 Hz, $^2J_{H5a\text{-}H5b}$ = 18.6 Hz, 1H, H-5a), 2.62 (m, 12H, $COCH_2CH_2N$ and $H_{piperazine}$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 191.38 (C-6), 171.93 (NHCO), 159.85 (C-6a), 151.43 (C-3a), 135.54 (C-1_{phenyl}), 134.46 (C-2_{phenyl}), 130.77 (C-6_{phenyl}), 129.60 (C-3_{phenyl}), 128.47 (C-4_{phenyl}), 126.68 (C-5_{phenyl}), 118.81 (C-1), 85.51 (C-3), 59.14 (C_{benzyl}), 53.41 ($COCH_2CH_2$), 52.61 (C-5), 52.09 (C-$3_{piperazine}$ and C-$5_{piperazine}$), 51.62 (C-$2_{piperazine}$ and C-$6_{piperazine}$), 43.52 (C-4), 31.52 ($COCH_2CH_2$). MS (m/z): 576.4 ($^+$M+2), 574.4 ($^+$M), 572.4 ($^+$M–2).

6.6. General experimental procedure for the synthesis of *84–92*

To a suspension of one of the compounds **66–75** (2 mmol) in methylene chloride (15 ml) at room temperature was added triethylamine (0.7 ml, 4.98 mmol). The resulting solution was then cooled to 0 °C and bromoacetyl bromide (0.22 ml, 2.49 mmol) solved in methylene chloride (5 ml) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C and for further 1 h at room temperature. The resulting mixture was evaporated under reduced pressure to give an oil which was then dissolved in methylene chloride and washed several times with water. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure.

6.6.1. 2-Bromo-N-(5,6-dimethoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)acetamide (*84*)

Yield: 65%. M.P. 208 °C. IR (KBr, cm^{-1}): 3273 (NH), 1697 (CO), 1655 (CO amide), 1592, 1502, 1469, 1044, 985, 861. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.16 (s, 1H, H-4), 6.99 (s, 1H, H-7), 6.77 (d, $^3J_{NH\text{-}H1c}$ = 8.0 Hz, 1H,NH), 5.60 (ddd, $^3J_{H1c\text{-}H2a}$ = 2.9 Hz, $^3J_{H1c\text{-}H2b}$ = 7.4 Hz, $^3J_{H1c\text{-}NH}$ = 8.0 Hz, 1H, H-1c), 3.98 (s, 3H, OMe), 3.94 (s, 3H, OMe), 3.20 (dd, $^3J_{H2b\text{-}H1c}$ = 7.4 Hz, $^2J_{H2b\text{-}H2a}$ = 18.9 Hz, 1H, H-2b), 2.48 (dd, $^3J_{H2a\text{-}H1c}$ = 2.9 Hz, $^2J_{H1a\text{-}H1b}$ = 18.9 Hz, 1H, H-2a), 1.43 (s, 2H, $COCH_2Br$). ^{13}C-NMR ($CDCl_3$) δ (ppm): 201.58 (C-3), 166.19 (NHCO), 156.14 (C-6), 150.93 (C-5), 148.03 (C-7a), 129.72 (C-3a), 106.73 (C-7), 103.73 (C-4), 4656.57 (OMe), 56.25 (OMe), 46.20 (C-1), 44.45 (C-2), 28.92 ($COCH_2Br$). MS (m/z): 329.0 ($^+$M+1), 327.0 ($^+$M–1).

6.6.2. 2-Bromo-N-(1,3-dimethyl-6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl)acetamide (*85*)

Yield: 77%. M.P. 203 °C. IR (KBr, cm^{-1}): 3420 (NH), 1701 (CO), 1645 (CO amide), 1559, 1436, 1218, 1070, 974. ^{1}H-NMR (DMSO d-6) δ (ppm): 8.91 (d, $^3J_{NH\text{-}H4c}$ = 8.4 Hz, 1H,NH), 5.19 (dt, $^3J_{H4c\text{-}H5a}$ = 3.4 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.4 Hz, 1H, H-4c), 3.85 (s, 2H, $COCH_2Br$), 3.38 (dd, $^3J_{H5b\text{-}H4c}$ = 8.4 Hz, $^2J_{H5b\text{-}H5a}$ = 18.8 Hz, 1H, H-5b), 2.70

(dd, $^{3}J_{H5a-H4c}$ = 3.4 Hz, $^{2}J_{H5a-H5b}$ = 18.8 Hz, 1H, H-5a), 2.49 (s, 3H, C1-Me), 2.46 (s, 3H, C3-Me). ^{13}C-NMR (DMSO d-6) δ (ppm): 195.52 (C-6), 165.44 (NHCO), 148.53 (C-6a), 139.24 (C-1), 138.98 (C-3), 129.71 (C-3a), 50.98 (C-5), 42.60 (CO*C*H$_2$Br), 42.57 (C-4), 12.84 (C1-*Me*), 12.01 (C3-*Me*). MS (m/z): 302.9 ($^+$M+1), 300.9 ($^+$M–1).

*6.6.3. 2-Bromo-N-(6-oxo-5,6-dihydro-4H-cyclopenta[b]thien-4-yl)acetamide (**86**)*

Yield: 64%. Oil. IR (KBr, cm^{-1}): 3286 (NH), 1700 (CO), 1660 (CO amide), 3077, 1538, 1430, 1290, 730. ^{1}H-NMR (CDCl$_3$) δ (ppm): 7.95 (d, $^{3}J_{H2-H3}$ = 4.6 Hz, 1H, H-2), 7.14 (d, $^{3}J_{H3-H2}$ = 4.6 Hz, 1H, H-3), 7.10 (d, $^{3}J_{NH-H4c}$ = 6.9 Hz, 1H,NH), 5.52 (dt, $^{3}J_{H4c-H5a}$ = 2.5 Hz, $^{3}J_{H4c-H5b}$ = $^{3}J_{H4c-NH}$ = 6.9 Hz, 1H, H-4c), 3.89 (s, 2H, COC*H*$_2$Br), 3.44 (dd, $^{3}J_{H5b-H4c}$ = 6.9 Hz, $^{2}J_{H5b-H5a}$ = 18.6 Hz, 1H, H-5b), 2.79 (dd, $^{3}J_{H5a-H4c}$ = 2.5 Hz, $^{2}J_{H5a-H5b}$ = 18.6 Hz, 1H, H-5a). ^{13}C-NMR (CDCl$_3$) δ (ppm): 193.15 (C-6), 166.43 (NHCO), 165.89 (C-3a), 142.24 (C-6a), 141.70 (C-3), 123.56 (C-2), 48.99 (C-5), 45.97 (C-4), 28.61 (CO*C*H$_2$Br). MS (m/z): 274.4 ($^+$M+1), 272.4 ($^+$M–1).

*6.6.4. 2-Bromo-N-(6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl)acetamide (**87**)*

Yield: 60%. M.P. 139 °C. IR (KBr, cm^{-1}): 3340 (NH), 1714 (CO), 1661 (CO amide), 2820, 1512, 1230, 1109, 760.^{1}H-NMR (CDCl$_3$) δ (ppm): 7.88 (s, 1H, H-1), 7.46 (s, 1H, H-3), 6.94 (d, $^{3}J_{NH-H4c}$ = 8.3 Hz, 1H,NH), 5.19 (m, 1H, H-4c), 4.20 (s, 2H, COC*H*$_2$Br), 3.49 (dd, $^{3}J_{H5b-H4c}$ = 8.0 Hz, $^{2}J_{H5b-H5a}$ = 18.9 Hz, 1H, H-5b), 2.90 (dd, $^{3}J_{H5a-H4c}$ = 3.3 Hz, $^{2}J_{H5a-H5b}$ = 18.9 Hz, 1H, H-5a). MS (m/z): 274.4 ($^+$M+1), 272.4 ($^+$M–1).

*6.6.5. 2-Bromo-N-(3-bromo-6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl)acetamide (**88**)*

Yield: 80%. M.P. 190 °C. IR (KBr, cm^{-1}): 3258 (NH), 1708 (CO), 1652 (CO amide), 1548, 1470, 1183, 1030, 772. ^{1}H-NMR (CDCl$_3$) δ (ppm): 7.80 (s, 1H, H-1), 6.93 (d, $^{3}J_{NH-H4c}$ = 8.1 Hz, 1H,NH), 5.42 (dt, $^{3}J_{H4c-H5a}$ = 3.6 Hz, $^{3}J_{H4c-H5b}$ = $^{3}J_{H4c-NH}$ = 8.1 Hz, 1H, H-4c), 3.94 (s, 2H, COC*H*$_2$Br), 3.53 (dd, $^{3}J_{H5b-H4c}$ = 8.1 Hz, $^{2}J_{H5b-H5a}$ = 19.3 Hz, 1H, H-5b), 2.88 (dd, $^{3}J_{H5a-H4c}$ = 3.6 Hz, $^{2}J_{H5a-H5b}$ = 19.3 Hz, 1H, H-5a). ^{13}C-NMR (CDCl$_3$) δ (ppm): 192.99 (C-6), 165.37 (NHCO), 150.40 (C-6a), 144.12 (C-3a), 126.00 (C-1), 107.45 (C-3), 51.64 (C-5), 44.90 (C-4), 28.61 (CO*C*H$_2$Br). MS (m/z): 354.8 ($^+$M+2), 352.8 ($^+$M), 350.8 ($^+$M–2).

*6.6.6. 2-Bromo-N-(2-bromo-4-oxo-5,6-dihydro-4H-cyclopenta[b]thien-6-yl)acetamide (**89**)*

Yield: 64%. M.P. 90 °C. IR (KBr, cm^{-1}): 3366 (NH), 1720 (CO), 1656 (CO amide), 2815, 1514, 1492, 1390, 1099, 752. ^{1}H-NMR (CDCl$_3$) δ (ppm): 7.40 (d, $^{3}J_{NH-H6c}$ = 7.2 Hz, 1H,NH), 7.00 (s, 1H, H-3), 5.40 (dt, $^{3}J_{H6c-H5a}$ = 2.5 Hz, $^{3}J_{H6c-H5b}$ = $^{3}J_{H6c-NH}$ = 7.2 Hz, 1H, H-4c), 3.49 (s, 2H, COC*H*$_2$Br), 3.22 (dd, $^{3}J_{H5b-H6c}$ = 7.2 Hz, $^{2}J_{H5b-H5a}$ = 18.3 Hz, 1H, H-5b), 2.79 (dd, $^{3}J_{H5a-H6c}$ = 2.5 Hz, $^{2}J_{H5a-H5b}$ = 18.3 Hz, 1H, H-5a). ^{13}C-NMR (CDCl$_3$) δ (ppm): 193.08 (C-6), 168.01 (C-6a), 166.82 (NHCO), 145.36 (C-3a), 121.53 (C-3), 120.53 (C-2), 47.46 (C-5), 46.61 (C-6), 28.69 (CO*C*H$_2$Br). MS (m/z): 355.9 ($^+$M+2), 353.9 ($^+$M), 351.9 ($^+$M–2).

*6.6.7. 2-Bromo-N-(2,3-dibromo-4-oxo-5,6-dihydro-4H-cyclopenta[b]thien-6-yl)acetamide (**90**)*

Yield: 62%. M.P. 102 °C. IR (KBr, cm^{-1}): 3305 (NH), 1714 (CO), 1659 (CO amide), 2926, 1530, 1390, 1108, 680. RMN ^{1}H (CDCl$_3$) δ (ppm): 7,35 (d, $^{3}J_{NH-H6c}$ = 7,0 Hz, 1H,NH); 5,45 (dt, $^{3}J_{H6c-H5a}$ = 2,7 Hz, $^{3}J_{H6c-H5b}$ = $^{3}J_{H6c-NH}$ = 7,0 Hz, 1H, H-6c); 3,93 (s, 2H, COC*H*$_2$Br); 3,44 (dd, $^{3}J_{H5b-H6c}$ = 7,0 Hz, $^{2}J_{H5b-H5a}$ = 18,4 Hz, 1H, H-5b); 2,79 (dd, $^{3}J_{H5a-H6c}$ = 2,7 Hz, $^{2}J_{H5a-H5b}$ = 18,4 Hz, 1H, H-5a). RMN ^{13}C (CDCl$_3$) δ (ppm): 190,94 (C-4); 167,08 (NHCO); 166,62 (C-6a); 142,01 (C-3a); 119,38 (C-2); 107,55 (C-3); 46,93 (C-5); 46,90 (C-6); 28,16 (CO*C*H$_2$Br). MS (m/z): 434.9 ($^+$M+3), 432.9 ($^+$M+1), 430.9 ($^+$M–1), 428.9 ($^+$M-3).

*6.6.8. 2-Bromo-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl)acetamide (**91**)*

Yield: 77%. M.P. 203 °C. IR (KBr, cm^{-1}): 3312 (NH), 1712 (CO), 1641 (CO amide), 2959, 1530, 1262, 1103, 800. ^{1}H-NMR (DMSO d-6) δ (ppm): 8.91 (d, $^{3}J_{NH-H4c}$ = 8.3 Hz, 1H,NH), 5.19 (ddt, $^{5}J_{Hc-H2Br}$ = 1.0 Hz, $^{3}J_{H4c-H5a}$ = 3.5 Hz, $^{3}J_{H4c-H5b}$ = $^{3}J_{H4c-NH}$ = 8.3 Hz, 1H, H-4c), 3.86 (d, $^{5}J_{H2Br-Hc}$ = 1.0 Hz, 2H, COC*H*$_2$Br), 3.08 (dd, $^{3}J_{H5b-H4c}$ = 8.3 Hz, $^{2}J_{H5b-H5a}$ = 18.0 Hz, 1H, H-5b), 2.70 (dd, $^{3}J_{H5a-H4c}$ = 3.5 Hz, $^{2}J_{H5a-H5b}$ = 18.0 Hz, 1H, H-5a). ^{13}C-NMR (DMSO d-6) δ (ppm): 193.17 (C-6), 165.70 (NHCO), 152.91 (C-6a), 142.36 (C-3a), 110.39 (C-1), 105.67 (C-3), 51.17 (C-5), 45.94 (CO*C*H$_2$Br), 43.50 (C-4). MS (m/z): 434.9 ($^+$M+3), 432.9 ($^+$M+1), 430.9 ($^+$M–1), 428.9 ($^+$M-3).

*6.6.9. 2-Bromo-N-(1,3-dichloro-6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl)acetamide (**92**)*

Yield: 77%. M.P. 180 °C. IR (KBr, cm^{-1}): 3310 (NH), 1717 (CO), 1640 (CO amide), 1527, 1527, 1490, 1398, 1105. ^{1}H-NMR (DMSO d-6) δ (ppm): 9.0 (large, 1H,NH), 5.26 (m, 1H, H-4c), 3.85 (s, 2H, COC*H*$_2$Br), 3.05 (m, 2H, H-5a and H-5b). ^{13}C-NMR (DMSO d-6) δ (ppm): 192.40 (C-6), 165.57 (NHCO), 148.76 (C-6a), 138.96 (C-3a), 123.90 (C-1), 119.25 (C-3), 50.66 (C-5), 29.05 (CO*C*H$_2$Br), 43.05 (C-4). MS (m/z): 343.8 ($^+$M+1), 341.8 ($^+$M–1).

*6.6.10. 4-Bromo-N-(1,3-dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl)butanamide (**93**)*

To a suspension of 6-amino-1,3-dibromo-5,6-dihydro-4H-cyclopenta[c]thiophen-4-one hydrochloride **74** (2 mmol) in methylene chloride (15 ml) at room temperature was added triethylamine (0.7 ml, 4.98 mmol), the resulting solution was then cooled to 0 °C and 4-bromobutyryl chloride (0,23 ml, 2.5 mmol) solved in methylene chloride (5 ml) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C and for other 3 h at room temperature. The resulting mixture was evaporated under reduced pressure to give an oil which was then dissolved in methylene chloride and washed several times with water. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. Yield: 73%. M.P. 182 °C. IR (KBr, cm^{-1}): 3412 (NH), 1719 (CO), 1638 (CO amide), 1547, 1472, 1132, 988, 692. ^{1}H-NMR (DMSO-d6) δ (ppm): 8.57 (d, $^3J_{NH\text{-}H4c}$ = 7.8 Hz, 1H,NH), 5.16 (m, 1H, H-4c), 3,50 (t, $^3J_{H4'\text{-}H3'}$ = 6.0 Hz, 2H, H-4′), 3.33 (dd, $^3J_{H5b\text{-}H4c}$ = 8.1 Hz, $^2J_{H5b\text{-}H5a}$ = 18.2 Hz, 1H, H-5b), 2.68 (d, $^2J_{H5a\text{-}H5b}$ = 18.2 Hz, 1H, H-5a), 2.22 (t, $^3J_{H2'\text{-}H3'}$ = 6.0 Hz, 2H, H-2′), 1.16 (q, $^3J_{H3'\text{-}H2'}$ = $^3J_{H3'\text{-}H4'}$ = 6.0 Hz, 2H, H-3). ^{13}C-NMR (DMSO-d6) δ (ppm): 193.14 (C-6), 170.52 (C-1′), 153.25 (C-6a), 142.08 (C-3a), 109.99 (C-1), 105.00 (C-3), 51.21 (C-5), 42.67 (C-4), 34.50 (C-4′), 32.24 (C-2′); 28.08 (C-3′). MS (m/z): 462.6 ($^+$M+3), 460.6 ($^+$M+1), 458.6 ($^+$M–1), 456.6 ($^+$M-3).

6.6.11. *N-(1,3-Dibromo-6-oxo-5,6-dihydro-4H-cyclopenta[c]thien-4-yl)acrylamide (**94**)*

To a suspension of 6-amino-1,3-dibromo-5,6-dihydro-4H-cyclopenta[c]thiophen-4-one hydrochloride **74** (2 mmol) in methylene chloride (15 ml) at room temperature was added triethylamine (0.7 ml, 4.98 mmol), the resulting solution was then cooled to 0 °C and 4-bromopropionyl chloride (0.25 ml, 2.5 mmol) solved in methylene chloride (5 ml) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C and for another 1 h at room temperature. The resulting mixture was evaporated under reduced pressure to give an oil which was then dissolved in methylene chloride and washed several times with water. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. Yield: 43%. M.P. 198 °C. IR (KBr, cm^{-1}): 3409 (NH), 1713 (CO), 1657 (CO amide), 3266, 1550, 1133, 957. ^{1}H-NMR (DMSO-d6) δ (ppm): 8.30 (d, $^3J_{NH\text{-}H4c}$ = 8.4 Hz, 1H,NH), 6.13 (m, 2H, CH=C*H$_2$*), 5.63 (dd, $^3J_{H\text{-}Hcis}$ = 3.9 Hz, $^3J_{H\text{-}Htrans}$ = 8.9 Hz, 1H, C*H*=CH$_2$), 5.26 (dt, $^3J_{H4c\text{-}H5a}$ = 3.5 Hz, $^3J_{H4c\text{-}H5b}$ = $^3J_{H4c\text{-}NH}$ = 8.4 Hz, 1H, H-4c), 3.41 (dd, $^3J_{H5b\text{-}H4c}$ = 8.4 Hz, $^2J_{H5b\text{-}H5a}$ = 18.8 Hz, 1H, H-5b), 2.70 (dd, $^3J_{H5a\text{-}H4c}$ = 3.5 Hz, $^2J_{H5a\text{-}H5b}$ = 18.8 Hz, 1H, H-5a). ^{13}C-NMR (DMSO-d6) δ (ppm): 193.16 (C-6), 164.05 (CONH), 153.06 (C-6a), 142.15 (C-3a), 131.14 (CH=*C*H$_2$), 126.02 (*C*H=CH$_2$), 110.39 (C-1), 105.39 (C-3), 51.39 (C-5); 42.82 (C-4). MS (m/z): 366.9 ($^+$M–2), 364.9 ($^+$M), 362.9 ($^+$M–2).

6.7. *General experimental procedure for the synthesis of **97** and **98***

A solution of arylaldehyde **95** or **96** (20 mmol) and ethyl N-piperazinecarboxylate (2.77 g, 20 mmol) in methanol (40 ml) was added to sodium cyanoborohydride (2.36 g, 40 mmol). Acetic acid (1 ml) was added and the stirred mixture was refluxed for one night. The solution was then diluted with ether (100 ml) and washed with an 1 N aqueous sodium hydroxide solution. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure.

6.7.1. *Ethyl 4-(1H-pyrrol-2-ylmethyl)piperazine-1-carboxylate (**97**)*

Yield: 82%. Oil. IR (KBr, cm^{-1}): 1699 (CO), 2807, 1432, 1242, 1004, 679. ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.16 (s, 1H,NH), 6.73 (dd, $^4J_{H5pyrrole\text{-}H3pyrrole}$ = 2.4 Hz, $^3J_{H5pyrrole\text{-}H4pyrrole}$ = 5.0 Hz, 1H, H-5$_{pyrrole}$), 6.12 (dd, $^3J_{H4pyrrole\text{-}H3pyrrole}$ = 2.9 Hz, $^3J_{H4pyrrole\text{-}H5pyrrole}$ = 5.0 Hz, 1H, H-4$_{pyrrole}$), 6.0 (large, 1H, H-3$_{pyrrole}$), 4.13 (q, $^3J_{H1\text{-}H2}$ = 7.1 Hz, 2H, C*H$_2$*CH$_3$), 3.49 (s, 2H,NC*H$_2$*pyrrole), 3.45 (t, $^3J_{H2\text{-}H3}$ = $^3J_{H6\text{-}H5}$ = 4.9 Hz, 4H, H-2 and H-6), 2.38 (t, $^3J_{H3\text{-}H2}$ = $^3J_{H5\text{-}H6}$ = 4.9 Hz, 4H, H-3 and H-5), 1.25 (t, $^3J_{H1\text{-}H2}$ = 7.1 Hz, 3H, CH$_2$C*H$_3$*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 155.51 (CO), 127.96 (C-2$_{pyrrole}$), 117.55 (C-5$_{pyrrole}$), 108.00 (C-4$_{pyrrole}$), 107.83 (C-3$_{pyrrole}$), 61.35 (*C*H$_2$CH$_3$), 55.42 (N*C*H$_2$pyrrole), 52.67 (C-3 and C-5), 43.68 (C-2 and C-6), 14.70 (Me). MS (m/z): 237.2 ($^+$M).

6.7.2. *Ethyl 4-[(2,5-dimethoxythien-3-yl)methyl]piperazine-1-carboxylate (**98**)*

Yield: 71%. Oil. IR (KBr, cm^{-1}): 1699 (CO), 2818, 2932, 1432, 1242, 1123, 686. ^{1}H-NMR ($CDCl_3$) δ (ppm): 5.78 (s, 1H, H-4$_{thiophene}$), 4.09 (q, $^3J_{H1\text{-}H2}$ = 7.1 Hz, 2H, C*H$_2$*CH$_3$), 3.76 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.49 (s, 2H,NC*H$_2$*thiophene), 3.43 (m, 8H, H$_{piperazine}$), 1.25 (t, $^3J_{H1\text{-}H2}$ = 7.1 Hz, 3H, CH$_2$C*H$_3$*). ^{13}C-NMR ($CDCl_3$) δ (ppm): 155.49 (CO), 154.51 (C-5$_{thiophene}$), 149.96 (C-2$_{thiophene}$), 116.23 (C-3$_{thiophene}$), 102.89 (C-4$_{thiophene}$), 63.07 (OMe), 61.27 (*C*H$_2$CH$_3$), 60.05 (OMe), 57.52 (N*C*H$_2$thiophene), 52.62 (C-3 and C-5), 43.60 (C-2 and C-6), 14.68 (Me). MS (m/z): 314.2 ($^+$M).

6.8. *General experimental procedure for the synthesis of **99** and **100***

Potassium hydroxide (5.61 g, 100 mmol) was slowly added into the reaction vessel containing a solution of compound **97** or **98** (10 mmol), water (4 ml) and methanol (12 ml). The reaction was heated under microwave irradiation to 100 °C and monitored by thin-layer chromatography. After the starting material had disappeared, the mixture was cooled, filtered and extracted with methylene chloride. The organic layer was separated, dried and evaporated under reduced pressure.

6.8.1. *1-(1H-Pyrrol-2-ylmethyl)piperazine (**99**)*

Yield: 100%. Oil, IR (KBr, cm^{-1}): 3370 (NH), 2826, 1540, 1419, 1271, 1113, 723. ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.84 (s, 1H,NH), 6.72 (d, $^3J_{H5pyrrole\text{-}H4pyrrole}$ = 2.4 Hz, 1H, H-5$_{pyrrole}$), 6.10 (m, 2H, H-3$_{pyrrole}$ and H-4$_{pyrrole}$), 3.48 (s, 2H,NC*H$_2$*pyrrole), 2.88 (t, $^3J_{H2\text{-}H3}$ = $^3J_{H6\text{-}H5}$ = 4.9 Hz, 4H, H-2 and H-6), 2.42 (m, 5H,NH, H-3 and H-5). ^{13}C-NMR ($CDCl_3$) δ (ppm): 127.42 (C-2$_{pyrrole}$), 117.52 (C-5$_{pyrrole}$), 107.92 (C-4$_{pyrrole}$), 107.44 (C-3$_{pyrrole}$), 55.69 (N*C*H$_2$pyrrole), 53.68 (C-2 and C-6), 45.41 (C-3 and C-5). MS (m/z): 165.4 ($^+$M).

6.8.2. *1-[(2,5-Dimethoxythien-3-yl)methyl]piperazine (**100**)*

Yield: 60%. Oil, IR (KBr, cm^{-1}): 3390 (NH), 28281590, 1455, 1232, 999, 729. ^{1}H-NMR ($CDCl_3$) δ (ppm): 5.83 (s, 1H, H-$4_{thiophene}$), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.31 (s, 2H,NCH_2thiophene), 2.90 (t, $^3J_{H2\text{-}H3}$ = $^3J_{H6\text{-}H5}$ = 4.9 Hz, 4H, H-2 and H-6), 2.4 (large, 4H, H-3 and H-5). ^{13}C-NMR ($CDCl_3$) δ (ppm): 154.43 (C-$5_{thiophene}$), 149.82 (C-$2_{thiophene}$), 116.63 (C-$3_{thiophene}$), 103.01 (C-$4_{thiophene}$), 63.13 (OMe), 60.05 (OMe), 57.70 (NCH_2thiophene), 53.67 (C-3 and C-5), 45.78 (C-2 and C-6). MS (m/z): 242.4 ($^+$M).

References

[1] See, for example, the whole issue of the following, Curr. Med. Chem. 7 (3) (2000).
[2] E-2020, Drugs Future 16 (1991) 16–18.
[3] A. Andreani, A. Cavalli, M. Granaiola, M. Guardigli, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, M. Recanatini, A. Roda, J. Med. Chem. 44 (2001) 4011–4014.
[4] P. Dallemagne, S. Rault, J.C. Pilo, M.P. Foloppe, M. Robba, Tetrahedron Lett. 44 (1991) 6327–6328.
[5] P. Dallemagne, J.C. Pilo, S. Rault, M. Robba, Bull. Soc. Chim. Fr. 130 (1993) 121–124.
[6] P. Dallemagne, S. Rault, M. Cugnon de Sévricourt, K.M. Hassan, M. Robba, Tetrahedron Lett. 27 (1986) 2607–2610.
[7] P. Dallemagne, S. Rault, M. Gordaliza, M. Robba, Heterocycles 26 (1987) 3233–3237.
[8] P. Dallemagne, A. Alsaïdi, M. Boulouard, S. Rault, M. Robba, Heterocycles 36 (1993) 287–294.
[9] O. Renault, P. Dallemagne, S. Rault, Pharm. Pharmacol. Commun. 4 (1998) 3–7.
[10] V.M. Rodionow, E.T. Malewinskaja, Chem. Ber. 59 (1926) 2952–2958.
[11] T.B. Johnson, J.E. Livak, J. Am. Chem. Soc. 58 (1936) 299–303.
[12] G.L. Ellman, K.D. Courtney, V. Andres, R.M. Featherstone, Biochem. Pharmacol. 7 (1961) 88–95.
[13] G. Kryger, I. Silman, J.L. Sussman, Struct. Fold. Des. 7 (1999) 297–307.
[14] C.M. Venkatachalam, X. Jiang, T. Oldfield, M. Waldman, J. Mol. Graph. Model. 4 (2003) 289–307.
[15] J.E. Ridley, M.C. Zerner, Theoret. Chim. Acta 42 (1976) 223–236.
[16] A.D. Bacon, M.C. Zerner, Theoret. Chim. Acta 53 (1979) 21–54.
[17] M.C. Zerner, G.H. Loew, R.F. Kirchner, U.T. Mueller-Westerhoff, J. Am. Chem. Soc. 102 (1980) 589–599.