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ORIGINAL ARTICLE

One-pot synthesis, biological evaluation, and docking study of new chromeno-annulated thiopyrano[2,3-*c*]pyrazoles

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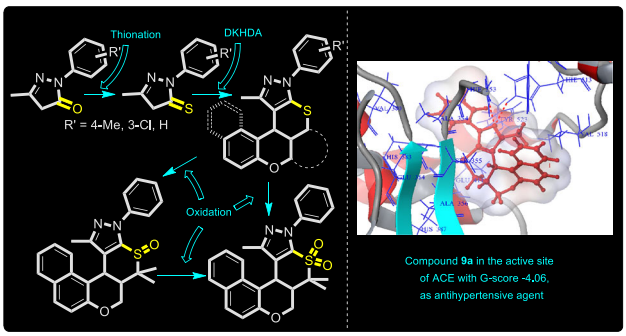
Abstract A one-pot synthesis of new chromeno-annulated thiopyrano[2,3-*c*]pyrazoles has been achieved through a domino-Knoevenagel–*hetero*-Diels–Alder reaction after combining various pyrazol-5-thiones with *O*-alkenyloxy/alkynyloxy-salicylaldehydes/naphthaldehydes in a Brønsted acidic ionic liquid, [Hmim]HSO_4, methylimidazolium hydrogen sulphate, under microwave irradiation. The method is simple and in many cases the isolated products did not require further purification. The central pyranothiopyranyl *cis*-fusion was confirmed by 2D NMR NOESY and single-crystal X-ray analysis suggesting that the *endo-E-Syn* transition state would be the most favored pathway of the reaction. Many heterocycles of this new series were found active against six bacterial and two fungal strains. In addition, all the compounds possess good anti-oxidant activity with the ferric reducing anti-oxidant power value >100 mmol/100g. All new structures were docked into active site of angiotensin I converting enzyme (ACE), assuming that the compounds possessed the anti-hypertensive activity potential on the basis of prediction of activity spectra of substances prediction results. Pyranyl ring oxygen in compound **9a** forms two hydrogen bonds with HIS353 and HIS513 residues in the active site of the ACE having good *G* score (−4.06) of this compound, comparable to that of the reference drug captopril (−4.93).

Graphical Abstract



Keywords Thiopyrano[2, 3-*c*]pyrazole · [Hmim]HSO_4 · Pyrazole-5-thione · Domino-Knoevenagel–*hetero*-Diels–Alder reaction · Microwave synthesis · Docking · Ionic liquid

Introduction

Heterocycles containing the pyranopyrazole-fused core are known for displaying a broad range of pharmacological properties, such as anti-inflammatory, analgesic, anti-hypertensive, ulcerogenic, anti-tubercular, anti-malarial, anti-hyperglycaemic, anti-tumor, anti-oxidant, anti-proliferative, vasodilating, and hypnotic [1–7]. Pyranopyrazoles have also an important role in agrochemical research due to their bactericidal, fungicidal, and herbicidal properties [8–10]. Pyrazole-carbohydrazides and pyrazoles substituted with sugars were reported as anti-cancer agents [11–15].

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Derivatives of thiopyran, and thiopyrano-fused pyrazoles and other heterocycles, on the other hand, constitute a class of sulfur heterocycle analogs of the possessing significant bioactivities [16–20]. RP 49356 is a K^+ channel opener [17]. Thiopyran derivatives are modulators of estrogen receptors, and possess a high dopamine receptor-binding affinity [21,22]. Pharmaceutically acceptable salts of tetrahydrothiopyrano-fused indoles are known for their psycho-analeptic and nootropic activities [19]. Thiopyranoquinolines exhibited interleukin-1 inhibitory activity. Some thiopyranopyrazoles showed non-steroidal anti-inflammatory activity, without producing gastric or renal toxicity, as selective COX-2 enzyme inhibitors [23,24]. Thus, the development of these heterocycles is of widespread interest, and synthetic activities targeting particularly their sulfur analogs certainly offer a way to access new bio-molecules to the medicinal and synthetic chemists.

The domino-Knoevenagel–*hetero*-Diels–Alder (DKHDA) reaction represents a noteworthy synthetic sequence, which has been widely used to synthesize pyran-heterocycles by assembling olefin-tethered aldehyde substrates with diketones or heterocyclic ketones including 5-pyrazolone [25–30]. The use of aldehyde substrates except for 5-alkenyl–sulfanyl–pyrazol–4-carbaldehyde has not been yet explored fully, leaving many new possibilities for thiopyranopyrazole synthesis [31–35]. Further, the Vilsmeier–Haack reaction is required to synthesize 5-alkenyl–sulfanyl–pyrazol–4-carbaldehyde substrate [23]. With a view to develop thiopyranopyrazole-heterocycles as new sulfur- containing scaffolds, it was aimed to use olefin-ether-tethered aldehyde substrates with 5-thiopyrazol by DKHDA strategy. As bioisosteres of pyranopyrazoles, known for their biological significance, all of the new thiopyranopyrazoles are anticipated to display newer and improved biological functions [36,37]. In general, combining one pharmacophore with others leads to the formation of new molecular scaffolds with improved biological functions. Further, sulfur-heterocycles are highly pursued synthetic targets due to their limited availability from natural sources [38–40].

Replacement of traditional toxic and volatile organic solvents with non-toxic and non-volatile ionic liquids (ILs) offers many synthetic advantages such as high thermal stability, low volatility, and recyclability of the reaction media [41–43]. Effective interactions between the IL and MW-radiation through high polarity and ionic conduction have been advantageous to promote many transformations [44–56]; the technique is called ILs on MW-assisted organic synthesis (MAOS). The *hetero*-Diels–Alder reaction [44] has also been successfully studied by this technique. MAOS [49,50] also reduces the solvent-emission, catalyst-reuse, and pollution problems to a larger extent [25–27,32].

To the best of our knowledge, butylmethylimidazolium tetrafluoroborate [bmim]BF_4 [52], its nitrate salts [53,54] and triethylammonium acetate (TEAA) [57–59] are the only ILs employed in the DKHDA reaction. For enhanced reactivity and better selectivity, the use of IL was therefore continued to improve this strategy. Recently, methylimidazolium hydrogen sulfate, [Hmim]HSO_4, has been used successfully in the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones, hydroquin azoline-2,5-diones/thiones [55], and 3,4-dihydropyrimidin-2-(1*H*)-ones [60]. This halogen-free, less-toxic/carbon-containing protic IL [55,56,60–64] also mediated synthesis of functionalized pyrroles [63], piperidines [64], pyrazolones [61], and α-aminonitriles [62]. As part of our continued effort and interest in the development of new polyheterocycles [57–59,65–67], we describe an efficient, one-pot synthesis of new thiopyrano [2,3-*c*]pyrazole-heterocycles in this work, via the DKHDA approach optimizing the reaction in [Hmim]HSO_4 under microwave irradiation.

Results and discussion

The ionic liquid [Hmim]HSO_4 was synthesized by reacting 1-methylimidazole with sulphuric acid according to the literature [55,62]. Salicylaldehyde **4a–h** and naphthaldehyde **5a–h** substrates were obtained by reacting salicylaldehyde **1** and 2-hydroxy-naphthaldehyde **2** with the corresponding alkenyl/alkynyl chloride or bromide **3a–h** in anhydrous K_2CO_3-suspended dimethylformamide (DMF) solution (Scheme 1) at room temperature as reported by our group [67]. Thionation of 1-(4-MePh/3-ClPh/Ph)-3-Me-5-pyrazolones with Lawesson's reagent in refluxing toluene, on the other hand, gave thiopyrazoles **6a–c** in quantitative yields [66].

Both the 2-allyloxy-naphthaldehyde **5a** and 2-prenyloxy-naphthaldehyde **5b** were reacted with thiopyrazole **6c** as model substrates to optimize the reaction condition (Table 1). In refluxing acetonitrile (entry 1) and xylene (entry 2), where no catalyst was used, the reaction failed to give the products even after 24 h. In presence of catalyst TBA-HS, averaged 40 % yield of **10a** and 58 % yield of **10b** were recorded after 12 and 7 h, respectively, in these solvents (entries 3, 4). Using the same catalyst under solvent-free environment at 140 °C, the yields of **10a** and **10b** could be improved up to 70 % (entry 5), in addition to reducing the reaction time. To further increase the product yield, we then examined the reaction in ionic liquid, TEAA, at 120 °C but failed to achieve remarkable development in this medium (entry 6). The use of ionic liquid, [Hmim]HSO_4, as a catalyst, did not work impressively under refluxing ethanol and toluene (entries 7, 8). The results were comparable to those obtained in refluxing acetonitrile or xylene (entries 3 and 4). Ionic liquid, [Hmim]HSO_4, was then tried as a reaction medium at 80 °C. A maximum of 82 % yield of **10a**/**10b** was achieved in

Scheme 1 Reagents and conditions: **i** DMF, K_2CO_3, RT, 8–10 h

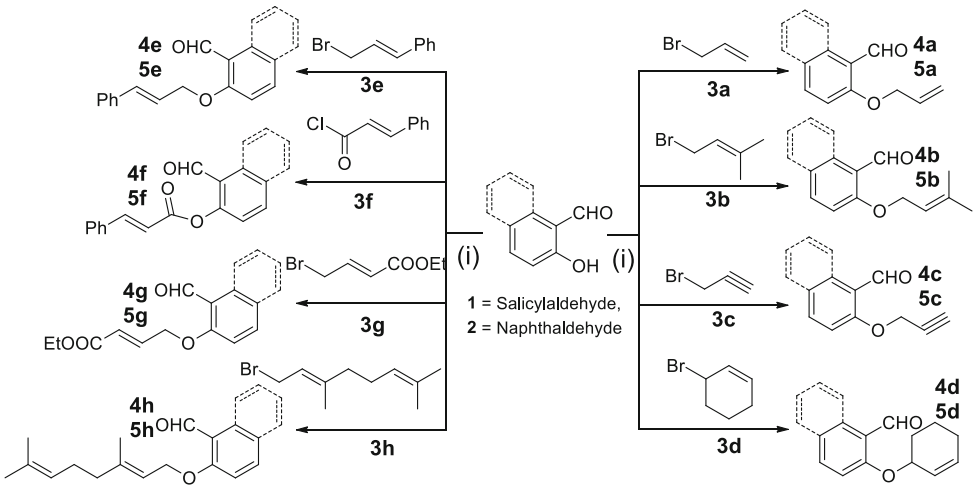


Table 1 Optimization of the DKHDA reaction under various conditions, **5a/5b** to **6c**

Entry	Solvent	Catalyst	Temp. (°C)	Time (h) **10a/10b**	Yield (%) **10a/10b**
1	Acetonitrile	–	Reflux	24	–
2	Xylene	–	Reflux	24	Trace
3	Acetonitrile	TBA–HS[a]	Reflux	12.0/7.0	38/56
4	Xylene	TBA–HS[a]	Reflux	12.0/7.0	42/59
5	–	TBA–HS[a]	140	3.5/2.0	68/72
6	–	TEAA[b]	120	3.5/2.5	64/68
7	Ethanol	[Hmim]HSO_4[c]	Reflux	12.0/5.0	56/66
8	Toluene	[Hmim]HSO_4[c]	Reflux	12.0/5.0	54/63
9	–	[Hmim]HSO_4[c]	80	1.5/1.0	80/82
10	MWI	[Hmim]HSO_4[c]	280 W	12 min	89/91

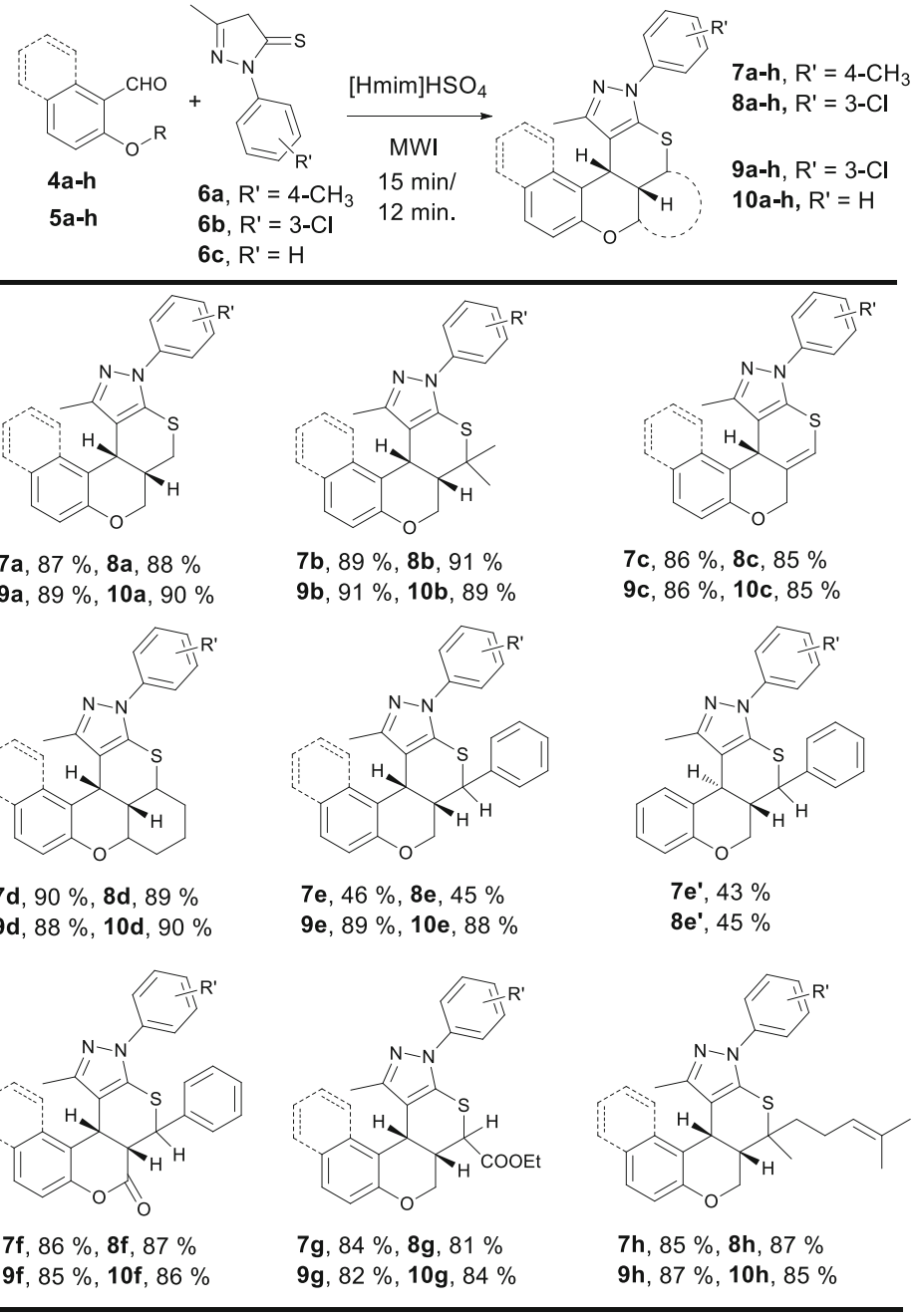
a = 0.25 equiv, b = 1.68 equiv., c = 0.5 equiv
MWI microwave irradiation, *TBA–HS* tetrabutylammonium hydrogen sulfate, *TEAA* triethylammonium acetate, [*Hmim*]HSO_4 methylimidazolium hydrogen sulfate

1.5 h (entry 9), which under microwave irradiation improved further to 90 % taking just 12 min to complete the reaction, at 280 W (entry 10). Syntheses of other heterocycles were then carried out following this optimal reaction condition (Scheme 2).

Figure 1 depicts a plausible mechanism of DKHDA reaction, showing the formation of Knoevenagel adduct, 1-thia-1,3-butadiene, from pyrazole-5-thione and the aldehyde substrate, along with traces of Michael adduct. These intermediates finally convert into a cyclized product via intramolecular *hetero*-Diels–Alder reaction. In the reaction medium, abstraction of a thiopyrazolone proton by ionic liquid forms an unstable methylimidazoliumthiopyrazolonate, which after reacting with the aldehyde transforms into Knoevenagel adduct via Michael adduct, formation releasing the ionic liquid simultaneously back into the medium. Knoevenagel adduct, under the influence of positive nitrogen of the ionic liquid, activates the terminal sulfur of 1-thia-2,3-butadiene, converting into the cyclized product finally.

Spectroscopic data: ^{1}H NMR, ^{13}C NMR, and IR spectra, of the heterocycles are in full agreement with their proposed structures.

Figure 2 shows the characteristic δ ppm values of the protons in their ^{1}H NMR which are part of the common skeleton in all heterocycles. Chemical shift values of the protons which belong to the thiopyran ring-fused fragment in different heterocycles, on the other hand, are mentioned in the periphery of the inner circle. Coupling constant $J = 2.8-5.2$ Hz value of a doublet observed at δ 4.06–4.95 ppm, assigned to the bridge-head proton H_a, confirmed its *cis*-orientation with the bridge-head proton H_b. Proton H_b gave a multiplet at δ 2.18–3.59 ppm. One of the thiopyranyl –SCH_2– protons gets de-shielded when the other proton is substituted by phenyl or the ester moiety, i.e., signal is shifting to higher δ ppm value. A more



Scheme 2 DKHDA products, **7, 8** and **9, 10**; as assemblies of pyrazole-5-thiones **6a–b** with salicylaldehyde-substrates **4a–h**, and as assemblies of **6b–c** with naphthaldehyde-substrates **5a–h**, respectively

pronounced effect in case of –SCH= proton was seen giving a signal at 6.02–6.07 δ ppm, for example, in compounds **7c–10c**. In this context, the carbocyclic ring fusion has little effect on the rest of the proton signals, for example, in compounds **7d–10d.** Pyranyl $-OCH_2$ protons gave a multiplet at δ 3.88–4.97 ppm. Similarly, protons of Me attached to the pyrazole showed a singlet at δ 1.37–2.53 ppm.

IR band in the 1005–1300 cm^{-1} range confirms the cyclic ether linkage of pyran ring. Likewise, the thiopyran ring was confirmed on the basis of characteristic band appearing in the region 600–700 cm^{-1} which was attributable to the C–S–C linkage. Molecular ion signals observed in the mass spectra were in agreement with the calculated molecular weights of the respective products.

The 2D NMR NOESY (Overhauser effect spectroscopy) of representative compound **9b** supported the *cis*-relationship between two bridge-head protons, H_a and H_b (Fig. 3).

Finally, the single-crystal X-ray diffraction data of representative **10a** were used to confirm unambiguously the presence of *cis*-fused pyranothiopyranyl core in all heterocycles. The compound crystallizes in triclinic space group P-1 with unit-cell parameters: $a = 8.3316(7)$, $b = 9.6125(6)$,

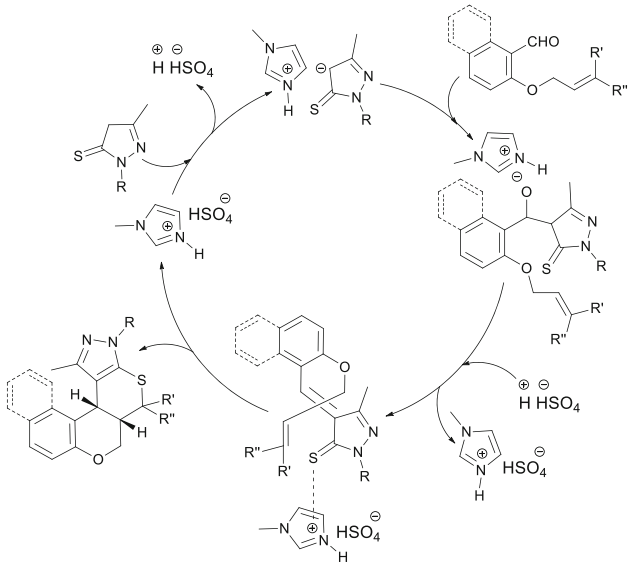


Fig. 1 A plausible mechanism of DKHDA reaction

c = 13.2921(10) Å, α = 79.966(5), β = 75.636(7), 65.755(7)°, Z = 2 (Fig. 4). The geometry of the molecule was calculated using the WinGX28 and PARST29 software packages [68,69].

Prediction of activity spectra for substances (PASS) study predicted higher anti-hypertensive activity for sulfoxide, **11**, and sulfone, **12**, than **10b** [70]. Synthesis of **11** and **12** has been depicted in Scheme 3 using *m*-CPBA as an oxidant.

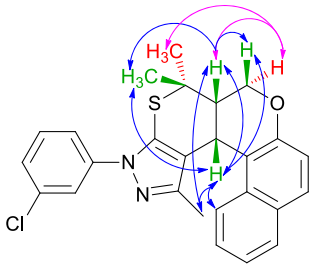


Fig. 3 Characteristic NOE's of **9b**

Biological evaluation and structure–activity relationship analysis

Table 2 lists the minimum inhibitory concentration (MIC) values of all compounds, which were measured against a panel of six different bacterial strains; three Gram +ve and three Gram −ve bacteria, and two fungal strains. The Table also incorporates % growth inhibition (GI of *M. Tuberculosis H37RV* bacteria) and ferric reducing anti-oxidant power (FRAP) values of all the compounds. From the MIC values, it could be seen that the compounds are almost equivalent to ampicillin in potency against at least one of the bacterial strains.

Sterically more bulky compounds were more active against Gram +ve bacteria like *C. tetani* and *B. subtilis*, while reverse was true for the less bulky compounds which showed better activity against Gram −ve bacteria. Compounds close

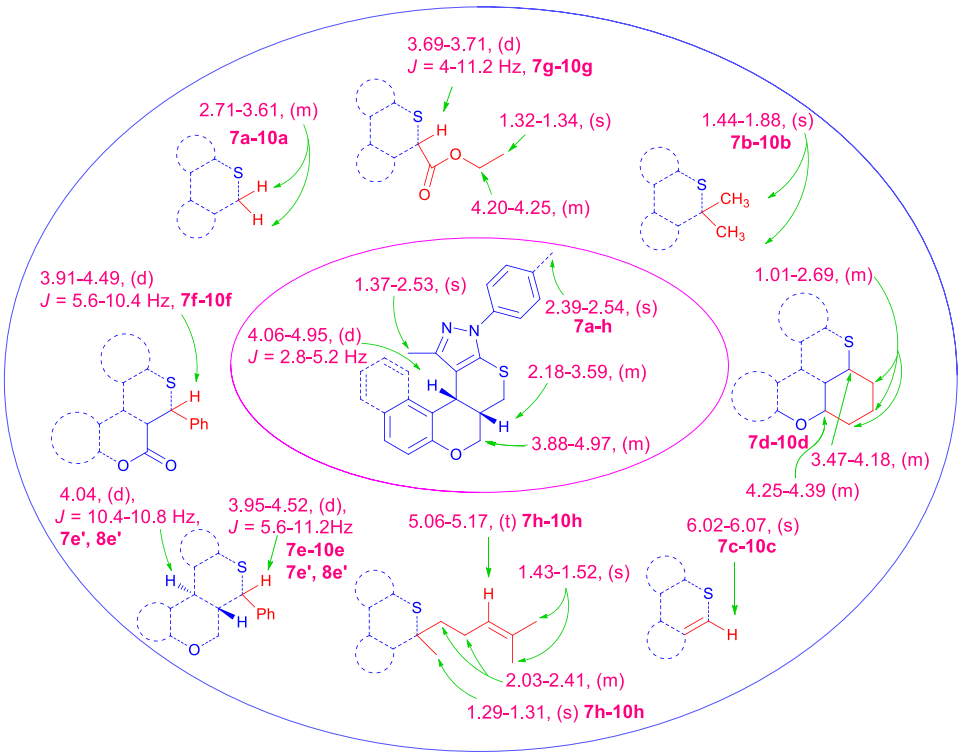
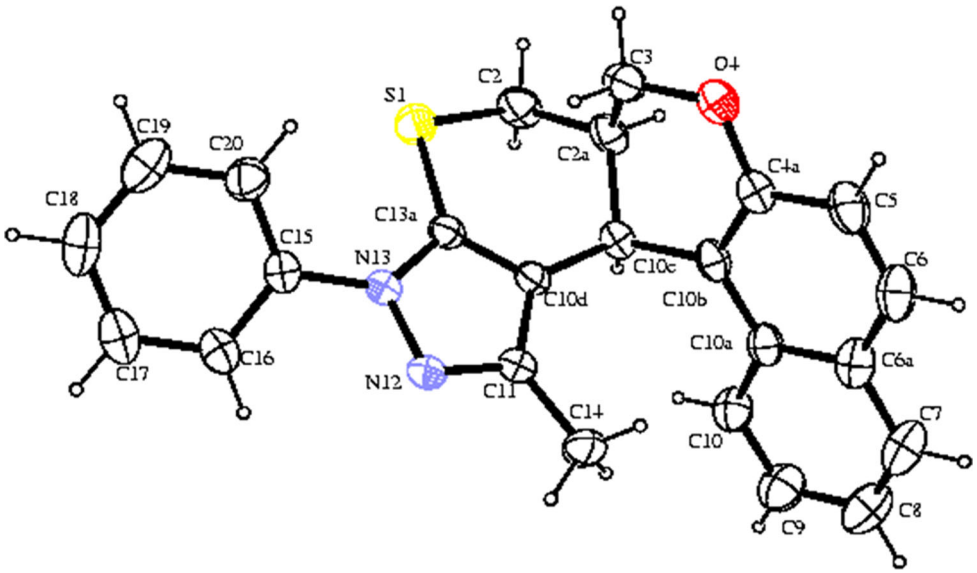
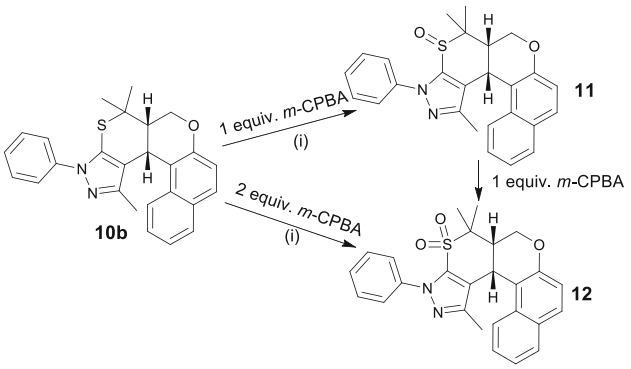


Fig. 2 ^{1}H NMR chemical shifts of all the compounds





Scheme 3 Reagents and conditions: (i) Dichloromethane, 0–5 °C (2h) and then at RT

to chloramphenicol in potency and those that were more potent than ampicillin against Gram −ve *E. coli* bacteria included **7f** and **10c**. Inhibitory effect of compound **8f** was found very near to the standard drugs chloramphenicol and ciprofloxacin both against the Gram +ve bacteria like *S. pneumonia*. MIC values of compounds **7e**, **7g**, **9c**, **9e**, **10a**, **10e**, and **10h** were found to be very close to ciprofloxacin against *C. tetani* bacteria. Norfloxacin-equivalent potency of compounds **8a–c**, **9a**, **9b**, **9d**, **9h**, and **10b,** was found against *B. subtilis* bacteria. Resistivity of compound **9b** was also found near to the standard drugs chloramphenicol and norfloxacin against *C. tetani* bacteria. Same was observed in the case of compound **7a**, but its activity was close to chloramphenicol and ciprofloxacin against *B. subtilis*. *S. pneumonia, S. Typhi, or V. cholera* bacteria were mostly the targets for compounds **7a**, **7b**, **7h**, **8b**, **9b**, and **10a**. Compound **7b** showed activity against all bacterial strains, and recorded a higher resistance, even more than the reference drugs except for gentamycin, against *C. tetani* and *S. typhi*. With a strong bacterial inhibition against Gram −ve *S. typhi*, compound **8b** revealed chloramphenicol-equivalent potency, with MIC value of 50 μg/mL. Compounds such as **7a** and **7h** were found active against *S. pneumonia* bacteria, with MIC value of 62.5 μg/mL, close to chloramphenicol and ciprofloxacin in potency.

Resistance power of **7b**, **8b**, **7f**, **9b**, and **10a** was noticeable against Gram −ve bacteria. Compounds **7b**, **9b**, and **10a** were active against Gram −ve *V. cholera*, resembling chloramphenicol in the resistivity. Overall, compound **7b** had very strong inhibitory effect against all bacterial strains. Compounds **7a**, **7h**, **8b**, **8d**, and **9e** were active against five of the bacterial species, whose MIC remained comparable to at least one of the standard drugs.

Anti-fungal activity of compounds **7e′**, **7f**, **8d**, **10a**, **10b**, **10e**, and **10f**, against *C. albicans* fungal strain, was found to be equal to griseofulvin. Compounds such as **7a**, **7d**, **7g**, **8b**, **8c**, **8e**, **8f**, **8g**, **9h**, and **10h** showed similar activity but emerged with relatively higher potential. Activity of all of the compounds against *A. fumigatus* fungal strain was found to be very poor.

Growth inhibition (GI) value of compounds **8f** and **10g** lying in the range of 90–99 % indicated good anti-tubercular activity of these candidates against *M. tuberculosis H37Rv* strain. Compounds **7e**, **9e**, **10f**, and **10h** exhibited good to moderate anti-tubercular activity with GI lying in the range of 80–90 %.

FRAP values of all the compounds were in the range of 220–300, indicating good anti-oxidant potential of these compounds.

The 3-Cl as R′ relative to H or 4-Me at phenyl ring of the pyrazol unit in many cases was found to be effective in improving the anti-bacterial profile. Compound **8f** in com-

Table 2 Anti-microbial, anti-tubercular, and anti-oxidant activities of thiopyrano[2,3-*c*]pyrazole-heterocycles, **7–10**

Compound	Anti-microbial activity (MIC, $\mu g\,mL^{-1}$)								Anti TB[a] activity (% inhibition)	Anti-oxidant activity[b] (FRAP value[c])
	Gram +ve bacteria			Gram −ve bacteria			Fungi			
	S.P.	C.T.	B.S.	S.T.	V.C.	E.C.	A.F.	C.A.		
7a	**62.5**	**250**	**62.5**	250	250	250	1000	**500**	20	220.48
7b	**125**	**25**	**250**	**25**	**50**	**100**	–	1000	77	239.96
7c	250	**250**	**250**	250	250	250	1000	1000	58	259.56
7d	250	**250**	**200**	250	200	250	1000	**500**	38	105.35
7e	250	**125**	**250**	200	250	200	500	1000	**86**	243.88
7e′	250	**250**	**200**	250	250	250	1000	**250**	45	280.07
7f	**100**	500	500	250	200	**62.5**	1000	**250**	58	289.12
7g	200	**125**	**250**	500	200	250	1000	**500**	61	290.12
7h	**62.5**	**250**	**250**	**125**	250	**100**	500	1000	74	234.63
8a	250	**250**	**125**	250	200	250	1000	–	12	221.49
8b	**125**	**250**	**100**	**50**	**100**	250	1000	**500**	54	243.18
8c	250	**250**	**125**	250	**125**	250	1000	**500**	62	234.43
8d	500	**200**	**250**	**100**	**100**	**100**	1000	**250**	45	165.07
8e	250	**250**	**200**	250	200	250	1000	**500**	47	239.66
8e′	200	**200**	**200**	200	**100**	250	500	1000	40	246.09
8f	**62.5**	**250**	500	200	250	250	1000	**500**	**91**	241.07
8g	250	**250**	**200**	**125**	200	250	500	**500**	55	251.92
8h	**125**	**250**	**250**	200	**125**	250	500	1000	65	300.18
9a	**125**	**250**	**100**	200	**100**	**125**	–	–	46	257.84
9b	**125**	**62.5**	**100**	250	**50**	200	–	1000	52	244.38
9c	250	**125**	**200**	**125**	250	250	500	1000	42	236.64
9d	**125**	**200**	**125**	200	200	200	500	1000	32	158.03
9e	**125**	**100**	**200**	**125**	250	**125**	500	1000	**85**	236.64
9f	500	**250**	**250**	200	250	250	500	1000	68	241.47
9g	250	**250**	**200**	200	**125**	250	500	1000	58	236.24
9h	200	**250**	**125**	250	200	250	–	**500**	74	221.76
10a	**100**	**125**	**250**	500	**62.5**	250	500	**250**	74	251.61
10b	500	**250**	**125**	200	500	250	1000	**250**	55	234.34
10c	500	500	500	200	200	**125**	250	–	35	254.13
10d	200	**200**	**250**	250	200	250	–	1000	20	114.00
10e	**125**	**100**	**250**	**125**	200	200	500	**250**	56	227.80
10f	200	**250**	**250**	200	200	**100**	1000	**250**	**88**	279.47
10g	200	**200**	**250**	200	500	200	500	1000	**90**	220.16
10h	500	**100**	**250**	250	200	250	1000	**500**	**85**	222.77
A	0.5	5	1	5	5	0.05	–	–	–	–
B	**100**	**250**	**250**	**100**	**100**	**100**	–	–	–	–
C	**50**	**50**	**50**	**50**	**50**	**50**	–	–	–	–
D	**50**	**100**	**50**	**25**	**25**	**25**	–	–	–	–
E	10	**50**	**100**	10	10	10	–	–	–	–
F	–	–	–	–	–	–	100	100	–	–
G	–	–	–	–	–	–	100	**500**	–	–
H	–	–	–	–	–	–	–	–	**99**	–

S.P. *Streptococcus pneumoniae*, C.T. *Clostridium tetani*, B.S. *Bacillus subtilis*, S.T. *Salmonella typhi*, V.C. *Vibrio cholerae*, E.C. *Escherichia coli*, A.F. *Aspergillus fumigatus*, C.A. *Candida albicans*

[*A*] Gentamycin, [*B*] Ampicillin, [*C*] Chloramphenicol, [*D*] Ciprofloxacin, [*E*] Norfloxacin, [*F*] Nystatin, [*G*] Griseofulvin, [*H*] Isoniazide

[a] Concentration of compounds used against *M. tuberculosis* H37Rv bacteria = 250 $\mu g/mL$, standard anti-microbials used: isoniazide (0.2 $\mu g/mL$)

[b] Concentration of compounds = 200 $\mu g/mL$ and standard: A.A. (ascorbic acid) = 176 $\mu g\,mL$

[c] A.A. mm/100 g sample

parison to **7f** against *S. pneumonia*, **8d** in comparison to **7d** against *S. typhi*, *V. cholera*, and *E. coli* and **8g** in comparison to **7g** against *S. typhi* bacteria were more potent. **8c**, **8d**, **8e′**, and **8h** against *V. cholera* were two times higher in inhibitory power than the corresponding **7c**, **7d, 7e′**, and **7h**. Anti-tubercular activity of compound **8f** was higher than **7f**. In a few cases, 4-Me group instead of 3′ Cl as R′ also improved the activity. Compound **7b** was found to be ten times more potent than **8b** in its resistivity toward *C. tetani*, *S. typhi*, and *V. cholera*. Compounds **7b** and **7h** are relatively more active than **8b** and **8h**, respectively. Compound **7f** was four times more active than **8f** in inhibition against *E. coli*. Compound **7e′** is four times more active than **8e′**, while inhibiting *C. albicans*. Anti-tubercular activity of **7e** was also higher than **8e.**

Naphthaldehyde-derived heterocycles also showed a similar trend of anti-bacterial profile when incorporated with 1-(3-ClPh)-5-thiopyrazolone unit. Compound **9b** was four times higher in activity than **10b** against both *S. pneumonia* and *C. tetani*. The difference in the resistivity was however ten times between these compounds against *V. cholera*. When compared to **10d**, compound **9d** has a little bit more inhibitory effect against *S. pneumonia* bacteria. Similarly, compound **9c** was four times higher in potency against *C. tetani*, compared to **10c**, and almost double in activity against *B. subtilis*. Compound **10a**, with 1-Ph at thiopyrazolone nitrogen, was also higher in activity compared to **9a** against *V. cholera*. Compounds **10a**, **10b**, **10e**, and **10f** in comparison to their respective chloro derivatives **9a**, **9b**, **9e**, and **9f** revealed the same pattern against the fungus *C. albicans*. Inhibition of growth of mycobacterium by compounds **10f**, **10g**, and **10h** (R′ is taken as H) was observed to be very strong relative to compounds **9f**, **9g**, and **9h** (3-Cl is taken as R). This trend was however seen to be reversed in case of compound **9e,** surprisingly.

Molecular docking studies

Anti-hypertensive activity was predicted for all the thiopyranopyrazoles when they were evaluated using prediction of activity spectra for substances (PASS) software [70] (Table 3). Thus, all the synthesized compounds were docked into the active site of angiotensin I-converting enzyme (ACE), assuming that their anti-hypertensive activity was originating by ACE inhibition. It is to be noted that although pyranopyrazoles are widely studied but any of them is yet to be reported for its anti-hypertensive activity.

The docking protocol was validated by observing orientation of the reference compound captopril in the active site of ACE. Captopril showed the highest *G* score of −4.93 and was observed to be oriented in the same manner as reported in the literature [71] as shown in Fig. 5a. One of the oxygen molecules of the carboxyl groups on the terminal proline formed three hydrogen bonds with GLN281, LYS511, and TYR520 residues, respectively. The *G* scores obtained through docking studies are shown in Table 4. Compound **9a** showed the highest *G* score (−4.06) among all the synthesized compounds, whereas compound **9g** showed

Table 3 Comparison of anti-hypertensive activity potential of thiopyrano[2,3-*c*]pyrazoles **7–10**, with their analogous pyrano[2,3-*c*]pyrazoles, based on Pa value

Compound	Pa (For anti-hypertensive activity)	
	Thiopyrano(2,3-*c*)pyrazole	Pyrano(2,3-*c*)pyrazole[a]
7a	0.638	0.460
7b	0.661	0.441
7c	0.690	0.472
7d	0.684	0.346
7e	0.734	0.435
7e′	0.734	0.435
7f	0.654	0.268
7g	0.636	0.415
7h	0.576	0.274
8a	0.594	0.422
8b	0.615	0.406
8c	0.650	0.436
8d	0.648	0.304
8e	0.688	0.400
8e′	0.688	0.400
8f	0.613	0.233
8g	0.599	0.380
8h	0.545	0.244
9a	0.538	0.345
9b	0.554	0.334
9c	0.589	0.368
9d	0.594	0.226
9e	0.634	0.330
9f	0.557	–
9g	0.550	0.318
9h	0.503	0.180
10a	0.608	0.416
10b	0.630	0.398
10c	0.668	0.433
10d	0.665	0.283
10e	0.708	0.393
10f	0.626	0.205
10g	0.611	0.372
10h	0.550	0.222
11	0.695	–
12	0.694	–

[a] Oxygen analogous of thiopyrano[2,3-*c*]pyrazole used for comparison

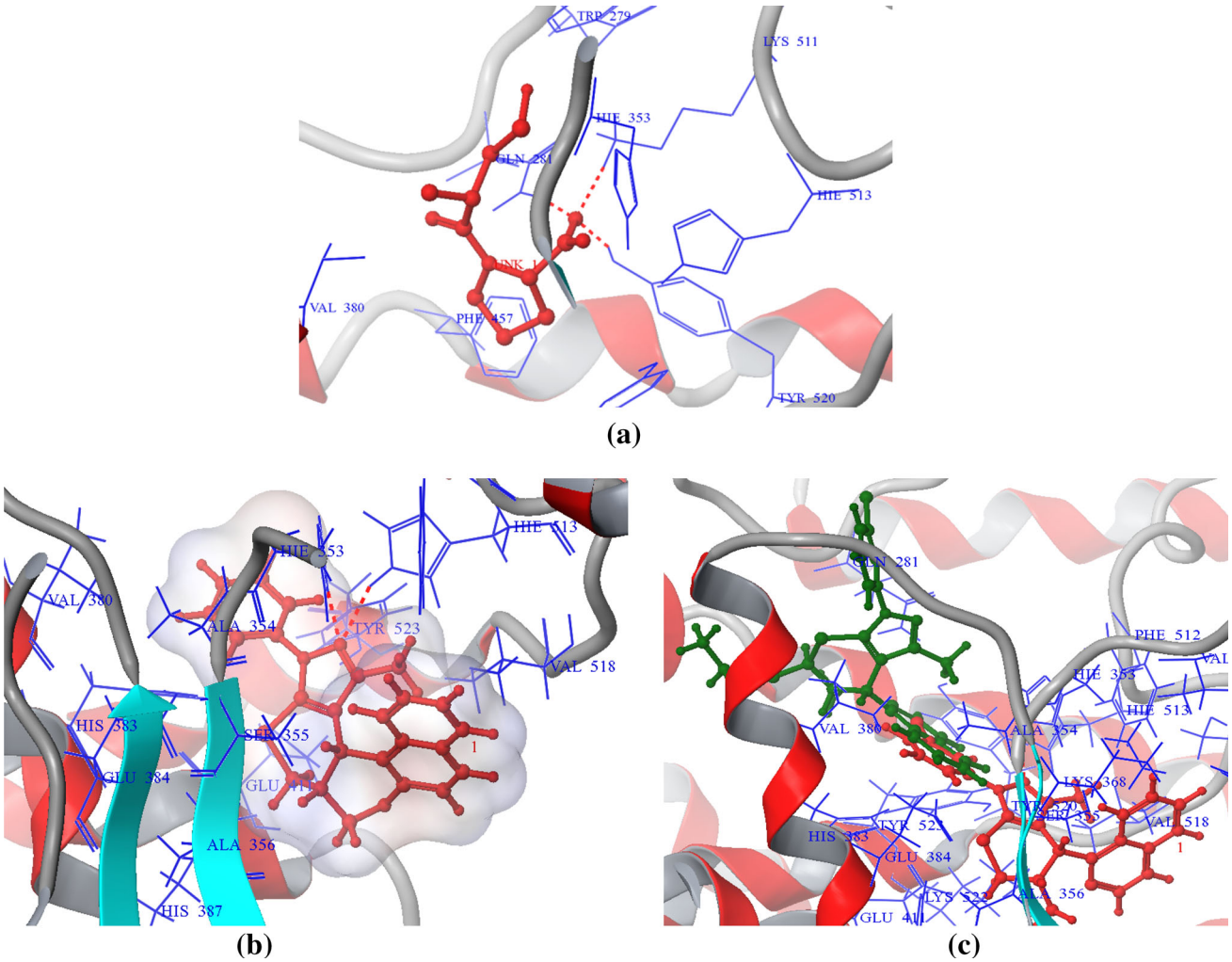


Fig. 5 **a** Orientation of captopril in the active site of ACE (PDB ID 4C2P), **b** Orientation of compound (**9a**) in the active site of ACE (PDB ID 4C2P), **c** Orientation of compound (**9a**) having the highest *G* score (−4.06) shown in *red color* and compound (**9g**) having the lowest *G* score (−2.20) shown in *green color* (H-bonds are shown in *red dotted lines*)

the lowest *G* score (−2.20). Pyranyl ring oxygen in compound **9a** formed two hydrogen bonds with HIS353 and HIS513 residues in the active site of the ACE as shown in Fig. 5b which might be a reason for it showing a good *G* score. The hydrogen bond distances from compound **9a** (N of 2nd position of pyrazole) with HIS353 and HIS513 residues were found to be 1.877 and 2.643 Å, respectively. Compound **9a** showed good contacts with HIS353, ALA354, SER355, HIS383, GLU384, HIS387, PHE512, VAL518, and TYR523 residues. Overlay structures of compound **9a** and compound **9g** are shown in Fig. 5c which clearly indicates orientation of compound **9g** in opposite side (away from the active site) to compound **9a**, and this could be one of the reasons of its poor *G* score. Drug like properties were calculated to see whether the synthesized compounds could become drugs or not. All the synthesized compounds were in the acceptable range for the following properties viz. molecular weight, no. of rotatable bonds, volume, H-bond acceptor, and PSA as shown in Table 4. In addition, all the compounds showed high (100 %) human oral absorption (HOA), except for compound **11**, and zero H-bond donor values. The HOA value of compound **11** is 95.686 %. Calculated log *P* value of some of the compounds was found to be in the acceptable range (compounds **7a**, **7b**, **7c**, **7f**, **7g**, **8a**, **8c**, **8f**, **8g**, **10a**, **10c**, **10g, 11** , and **12**) as shown in Table 4.

Conclusion

In conclusion, we demonstrated the DKHDA reaction assembling the thiopyrazole and salicylaldehyde/naphthaldehyde-based substrates in IL, [Hmim]HSO_4, under the microwave irradiation. The method did not involve chromatographic

Table 4 *G* score and other parameters of the docked compounds (**7a–12**)

Compound	M.W.	Volume	No. of rotatable bonds	HBA	QPlogPo/w	PSA	*G* score
7a	348.46	1073.33	0	2	5.79	23.99	−3.47
7b	376.51	1164.55	0	2	6.34	23.90	−3.28
7c	346.44	1070.84	0	2	5.84	24.15	−3.05
7d	388.52	1196.12	0	2	6.57	23.18	−2.73
7e	424.55	1293.87	0	2	7.40	24.14	−2.84
7e′	424.55	1287.27	0	2	7.35	23.94	−3.26
7f	438.54	1275.52	0	3	6.10	49.89	−2.86
7g	420.52	1289.44	2	4	5.89	57.02	−3.20
7h	444.63	1424.72	3	2	8.04	24.04	−3.22
8a	368.88	1057.39	0	2	5.97	23.98	−3.44
8b	396.93	1148.63	0	2	6.52	23.89	−2.79
8c	366.86	1051.77	0	2	6.00	24.08	−3.94
8d	408.94	1180.19	0	2	6.75	23.17	−3.08
8e	444.97	1277.98	0	2	7.58	24.13	−3.19
8e′	444.97	1271.20	0	2	7.53	23.93	−3.09
8f	458.96	1259.76	0	3	6.28	49.88	−2.82
8g	440.94	1273.50	2	4	6.07	57.01	−2.91
8h	465.05	1408.80	3	2	8.22	24.03	−2.26
9a	418.94	1181.68	0	2	6.87	24.19	−4.06
9b	446.99	1268.44	0	2	7.40	23.65	−3.03
9c	416.92	1177.10	0	2	6.88	24.26	−2.95
9d	459.00	1297.51	0	2	7.58	24.11	−2.63
9e	495.03	1391.76	0	2	8.37	22.19	−2.20
9f	509.02	1383.26	0	3	7.16	49.64	−2.70
9g	491.00	1394.72	2	4	6.95	55.95	−2.20
9h	515.11	1530.34	3	2	9.09	24.27	−2.56
10a	384.49	1137.61	0	2	6.36	24.20	−3.78
10b	412.54	1224.38	0	2	6.90	23.66	−3.66
10c	382.47	1133.02	0	2	6.39	24.25	−3.58
10d	424.55	1252.97	0	2	7.07	24.12	−2.89
10e	460.59	1348.06	0	2	7.87	22.20	−3.09
10f	474.57	1339.45	0	3	6.66	49.65	−3.64
10g	456.55	1350.65	2	4	6.45	55.96	−2.36
10h	480.66	1486.28	3	2	8.59	24.28	−2.65
11	428.54	1253.92	0	2	4.89	41.24	−3.92
12	444.54	1267.61	0	3	4.80	57.89	−3.54

G score of the standard drug: Captopril = −4.93, Enalapril = −4.63

purification for product isolation in many cases. Recyclability of the IL was confirmed at least three times without loss of its efficiency. All new chromen-annulated *cis*-fused thiopyranopyrazoles were evaluated biologically, in vitro. Compounds **7a**, **7b**, **7f**, **7h**, **8b**, **8f**, **9b** and **10a** showed good anti-bacterial activity with MIC values in the range of 62.5–25 μg/mL, which were better than the standard ampicillin. The compounds also exhibited anti-hypertensive activity potential as indicated by their docking study in the active site of ACE. This study highlighted compound **9a** as a lead molecule with good orientation in the active site of ACE.

Experimental section

General

All solvents and reagents were used as supplied from the commercial sources. Recorded melting points are uncor-

rected. IR spectra were recorded on Shimadzu FT-IR 8401 spectrometer using KBr discs, and are expressed in wave numbers (cm^{-1}). All microwave heating experiments were performed in a closed system, on Catalyst Scientific Microwave Oven model CATA-R (2.45 GHz, 140–700 Watts) from Catalyst^{TM} Systems, Pune, India. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR as solutions in $CDCl_3$, unless and otherwise indicated. Chemical shifts are expressed in parts per million (ppm, δ) and referenced to the residual protic solvent. Coupling constants are expressed in Hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. The degree of substitution (C, CH, CH_2, and CH_3) was determined by the APT method. The ESI mass spectra were measured on Shimadzu LCMS-2010 spectrometer. TLC was performed on Merck 60 F254 precoated silica plates, and spots were detected either by means of UV (254, 366 nm) or permanganate solution [$KMnO_4$ (3 g), K_2CO_3 (20 g), NaOH (5 mL, 5 % in H_2O), H_2O (300 mL)] or 2,4-dinitrophenylhydrazine solution [2,4-DNP (12 g), Conc. H_2SO_4 (6 mL), Water (8 mL), EtOH (20 mL)].

All the computational studies were carried out using Maestro 9.0 version Schrödinger, LLC, New York, NY, USA [72]. Structures of molecules were built using Chem Draw Ultra 8.0 [73] and structures were converted into Mol2 format using Open Babel 2.3.0 [74]. The structures were imported in Maestro 9.0. All the structures were minimized using OPLS 2005 force field in standard option Ligprep in Maestro 9.0 (LigPrep, version 2.3). Two well-known ACE inhibitors, captopril and enalapril, were also minimized as per the same protocol and added to the dataset as reference compounds. These minimized structures were utilized for docking in the active site of ACE using Glide 5.5 (Maestro 9.0). The crystal structure of ACE co-crystallized with captopril (PDB ID 4C2P) was downloaded from RCSB Protein Data Bank (PDB) [75]. Receptor grid was prepared, using standard option Receptor Grid Generation in Maestro 9.0. The van der Waals radii of the ligands were scaled to 0.9 with partial charges cut-off to 0.25 [76,77]. All the minimized compounds were docked rigidly by standard precision method. Different properties of the compounds were calculated using standard option Qikprop in Maestro 9.0. Acceptable range or recommended values for different properties, i.e., for molecular weight 130.0–725.0, number of rotatable bonds 0–15, volume 500.0–2000.0, number of H-bond donor 0.0–6.0, number of acceptor bond 2.0–20, log P −2.0–6.5, and polar surface area 7.0–200.0. Percentage human oral absorption indicates > 80% as high and < 25% as poor [QikProp, version 3.2, Schrödinger, LLC, New York, NY, 2009].

*General experimental procedure for synthesis of thiopyrano[2,3-c] pyrazoles (**7a–h, 8a–h, 9a–h, 10a–h**):*

A mixture of equimolar amounts (2 mmol) of *O*-alkenylated/alkynylated salicylaldehyde/naphthaldehyde and pyrazole-5-thione, taken in 0.5 equiv. of ionic liquid [Hmim]HSO_4 in a round-bottom flask was irradiated under microwave irradiation at 280 W for 15/12 min, respectively, until the reaction was confirmed as complete by TLC. The reaction mass was washed with water (25 mL) after cooling it to room temperature. The aqueous layer containing ionic liquid was washed by ether in order to remove undesired impurities, followed by drying under vacuum, which further facilitated recovery of the ionic liquid. Ethanol was added to the insoluble crude mass to allow the product to crystallize into pure form. The final product was then filtered. Chromatographic purification was required to isolate some of the compounds.

*Spectroscopy data of compounds **7–10, 11, 12**:*

1-*Methyl*-3-(*p-tolyl*)-5,5*a*,6,11*b-tetrahydro*-3*H-chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**7a**): White solid, yield 87 %, mp 111–113 °C, IR (ν_{max}, cm^{-1}): 3049, 2926, 1602, 1505, 1248, 1072, 1002, 765, 698, 661; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3 of pyrazole), 2.46 (s, 4H, 5a-H & CH_3 of phenyl ring), 2.90 (d, J = 12.8 Hz, 1H, 5-H), 3.26 (t, J = 12 Hz, 1H, 5-H), 4.24 (d, J = 4.4 Hz, 1H, 11b-H), 4.44 (d, J = 11.2 Hz, 1H, 6-H), 4.54 (d, J = 11.2 Hz, 1H, 6-H), 6.82–7.50 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.6, 21.1, 25.6, 32.8, 32.1, 70.2, 114.5, 115.9, 121.4, 122.3, 123.7, 127.6, 128.4, 129.0, 129.7, 136.5, 138.5, 150.1, 152.0; ESI-MS (m/z): 349.1 $(M+H)^+$, Anal. Calcd for $C_{21}H_{20}N_2OS$: C, 72.38; H, 5.79; N, 8.04; S, 9.20; Found: C, 72.49; H, 5.48; N, 7.89; S, 8.96.

1,5,5-*Trimethyl*-3-(*p-tolyl*)-5,5*a*,6,11*b-tetrahydro*-3*H-chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**7b**): White solid, yield 89 %, mp 118–120 °C, IR (ν_{max}, cm^{-1}): 3063, 2969, 2921, 1603, 1496, 1451, 1252, 1031, 1020, 762, 691, 674; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81 (s, 3H, 5-CH_3), 1.88 (s, 3H, 5-CH_3), 2.41 (s, 3H, CH_3 of pyrazole), 2.45 (s, 3H, CH_3 of phenyl ring), 2.52 (m, 1H, 5a–H), 4.50 (d, J = 4.4 Hz, 1H, 11b-H), 4.57 (t, J = 10.4 Hz, 1H, 6-H), 4.74 (dd,J = 6.4, J = 2.0 Hz, 1H, 6-H), 7.18–7.90 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 21.3, 26.5, 29.8, 32.4, 40.5, 45.6, 65.7, 110.4, 115.1, 118.7, 121.2, 123.4, 126.7, 128.0, 129.2, 130.8, 136.6, 140.3, 148.6, 153.2; ESI-MS (m/z): 377.2 $(M+H)^+$, Anal. Calcd for $C_{23}H_{24}N_2OS$: C, 73.37; H, 6.42; N, 7.44; S, 8.52; Found: C, 73.04; H, 6.14; N, 7.21; S, 8.78.

1-*Methyl*-3-(*p-tolyl*)-6,11*b-dihydro*-3*H-chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**7c**): White solid, yield 86 %, mp 154–156 °C, IR (ν_{max}, cm^{-1}): 3056, 2931, 2854, 1694, 1644, 1595, 1549, 1504, 1292, 1273, 1242, 1218, 1181, 1148, 1104, 1074, 873, 840, 822, 803, 779, 757, 697, 669, 638, 618; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3 of pyrazole), 2.42 (s, 3H, CH_3 of phenyl ring), 4.77 (d, J = 12 Hz, 1H, 6-H), 4.94–4.97 (m, 2H, 6-H & 11b-H), 6.07 (s, 1H, 5-H), 6.89–7.47 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.6, 21.1, 35.2, 72.7, 109.4, 110.0, 117.0, 121.0, 122.7, 125.6, 127.5, 127.8, 128.0, 128.3, 129.9, 136.8, 137.4, 148.8, 153.9; ESI-MS (m/z): 347.3 $(M+H)^+$, Anal. Calcd for $C_{21}H_{18}N_2OS$: C, 72.80; H, 5.24; N, 8.09; S, 9.26; Found: C, 73.09; H, 4.87; N, 8.24; S, 9.39.

1-*Methyl*-3-(*p-tolyl*)-3,4*a*,5,6,7,7*a*,7*b*,12*b-octahydro-xantheno*[9′,9*a*′,1′:4,5,6]*thiopyrano*[2,3-*c*]*pyrazole* (**7d**): White solid, yield 90 %, mp 242–244 °C, IR (ν_{max}, cm^{-1}): 3061, 3035, 2955, 2929, 2899, 1608, 1581, 1512, 1450, 1302, 1279, 1230, 1204, 1179, 1150, 1108, 1081, 1070, 866, 850, 824, 780, 760, 734, 699, 654, 628, 610; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58–2.13 (m, 5H, CH_2), 2.29–2.33 (m, 1H, 7b-H), 2.37 (s, 3H, CH_3 of pyrazole), 2.54 (s, 3H, CH_3 of phenyl ring), 2.65–2.69 (m, 1H, CH_2), 4.04–4.06 (d, 1H, J = 4.4 Hz, 12b-H), 4.14–4.18 (m, 1H, 4a-H), 4.29–4.30 (d, 1H, J = 2.8 Hz, 7a-H), 6.80–7.36 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 17.1, 20.9, 28.6, 29.7, 33.2, 39.9, 47.4, 74.3, 116.7, 121.2, 122.0, 122.2, 126.6, 126.9, 129.3, 129.4, 135.8, 136.4, 136.7, 146.4, 156.3; ESI-MS (m/z): 389.1 $(M+H)^+$, Anal. Calcd for $C_{24}H_{24}N_2OS$: C, 74.19; H, 6.23; N, 7.21; S, 8.25; Found: C, 73.87; H, 6.47; N, 7.36; S, 8.48.

1-*Methyl*-5-*phenyl*-3-(*p-tolyl*)-5,5*a*,6,11*b-tetrahydro*-3*H-chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**7e**): White solid, yield 46 %, mp 266–268 °C, IR (ν_{max}, cm^{-1}): 3055, 3033, 2948, 2920, 2861, 1614, 1588, 1519, 1241, 1209, 1177, 1150, 1099, 1062, 839, 819, 793, 777, 750, 710, 685, 646, 609; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H, CH_3 of pyrazole), 2.51 (s, 3H, CH_3 of phenyl ring), 2.61–2.66 (m, 1H, 5a-H), 3.97–4.01 (m, 1H, 6-H), 4.24–4.27 (m, 1H, 6-H), 4.43 (d, J = 4.4 Hz, 1H, 11b-H), 4.52 (d, J = 11.2 Hz, 1H, 5-H), 6.86–7.52 (m, 13H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 21.3, 33.2, 37.2, 43.9, 67.7, 114.0, 116.6, 121.1, 122.2, 124.0, 128.1, 128.5, 128.8, 128.9, 129.6, 129.6, 132.0, 136.8, 137.1, 137.8, 148.5, 153.1; ESI-MS (m/z): 425.2 $(M+H)^+$, Anal. Calcd for $C_{27}H_{24}N_2OS$: C, 76.38; H, 5.70; N, 6.60; S, 7.55; Found: C, 76.51; H, 5.62; N, 6.94; S, 7.34.

1-*Methyl*-5-*phenyl*-3-(*p-tolyl*)-5,5*a*,6,11*b-tetrahydro*-3*H-chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**7e′**): White solid, yield 43 %, mp 197–199 °C, IR (ν_{max}, cm^{-1}): 3055, 3034, 2949, 2921, 2860, 1614, 1588, 1518, 1241, 1208, 1176, 1150, 1099, 1060, 839, 818, 793, 777, 751, 710, 685, 648, 611; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3 of pyrazole), 2.39 (s, 3H, CH_3 of phenyl ring), 2.84–2.94 (m, 1H, 5a-H), 3.88–3.94 (m, 1H, 6-H), 3.97–4.01 (m, 1H, 6-H), 4.04 (d, J = 10.4 Hz, 1H, 11b-H), 4.11 (d, J = 10.8 Hz, 1H, 5-H), 6.90–7.43 (m, 13H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 21.2, 37.5, 46.6, 50.7, 71.7, 112.6, 116.8, 120.6, 122.7, 124.8, 127.8, 128.1, 128.6, 128.8, 129.2, 129.7, 133.3, 136.7, 136.7, 137.8, 148.7, 155.3; ESI-MS (m/z): 425.2 $(M+H)^+$, Anal. Calcd for $C_{27}H_{24}N_2OS$: C, 76.38; H, 5.70; N, 6.60; S, 7.55; Found: C, 76.45; H, 5.58; N, 6.90; S, 7.37.

1-*Methyl*-5-*phenyl*-3-(*p-tolyl*)-5,5*a-dihydro*-3*H-chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazol*-6(11*bH*)-*one* (**7f**): White solid, yield 86 %, mp 217–219 °C, IR (ν_{max}, cm^{-1}): 3011, 2921, 2850, 1771, 1691, 1627, 1541, 1501, 1312, 1275, 1259, 1201, 1174, 1108, 1082, 1074, 866, 836, 771, 738, 714, 699, 646; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H, CH_3 of pyrazole), 2.39 (s, 3H, CH_3 of phenyl ring), 3.56–3.59 (m, 1H, 5a-H), 4.49 (d, J = 9.6 Hz, 1H, 5-H), 4.54 (d, J = 4.4 Hz, 1H, 11b-H), 7.12–7.51 (m, 13H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.5, 21.0, 32.6, 43.4, 46.9, 109.4, 117.0, 122.7, 124.6, 125.1, 128.4, 129.0, 129.1, 129.2, 129.2, 129.8, 132.0, 135.8, 136.8, 137.4, 148.5, 149.8, 166.6; ESI-MS (m/z): 439.2 $(M+H)^+$, Anal. Calcd for $C_{27}H_{22}N_2O_2S$: C, 73.95; H, 5.06; N, 6.39; S, 7.31; Found: C, 73.64; H, 4.88; N, 6.63; S, 7.53.

*Ethyl*1-*methyl*-3-(*p-tolyl*)-5,5*a*,6,11*b-tetrahydro*-3*H-chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole*-5-*carboxylate* (**7g**): Yellow oil, yield 84 %, IR (ν_{max}, cm^{-1}): 3160, 3061, 2971, 2934, 1740, 1671, 1631, 1600, 1548, 1287, 1239, 1172, 1166, 1091, 1059, 1031, 860, 824, 752, 704, 660, 620; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 3H, 4′-CH_3), 2.38 (s, 3H, CH_3 of pyrazole), 2.42 (s, 3H, CH_3 of phenyl ring), 2.44 (m, 1H, 5a-H), 3.66 (d, J = 11.2 Hz, 1H, 5-H), 4.20 (m, 2H, Two 3′-H), 4.31 (m, 1H, 6-H), 4.39 (d, J = 4 Hz, 1H, 11b-H), 4.57 (m, 1H, 6-H), 6.83–7.80 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 14.2, 20.7, 28.9, 35.6, 45.7, 63.0, 64.9, 118.5, 120.1, 123.4, 124.8, 125.6, 127.3, 128.0, 128.8, 129.3, 132.5, 136.8, 142.5, 150.8, 171.2; ESI-MS (m/z): 421.2 $(M+H)^+$, Anal. Calcd for $C_{24}H_{24}N_2O_3S$: C, 68.55; H, 5.75; N, 6.66; S, 7.63; Found: C, 68.31; H, 5.53; N, 6.38; S, 7.47.

1,5-*Dimethyl*-5-(4-*methylpent*-3-*en*-1-*yl*)-3-(*p-tolyl*)-5,5*a*,6,11*b-tetrahydro*-3*H-chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**7h**): Yellow oil, yield 85 %, IR (ν_{max}, cm^{-1}): 3060, 2948, 2921, 2861, 1639, 1610, 1514, 1292, 1252, 1230, 1164, 1080, 814, 739, 670, 658, 612; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H, 5-CH_3), 1.46 (s, 3H, 4′-CH_3), 1.51 (s, 3H, 4′-CH_3), 2.10 (m, 2H, 1′-H & 2′-H), 2.23 (m, 2H, 1′-H & 2′-H), 2.44 (m, 1H, 5a-H), 2.48 (s, 3H, CH_3

of pyrazole), 2.51 (s, 3H, CH_3 of phenyl ring), 4.04 (t, 1H, 6-H), 4.13 (m, 1H, 6-H), 4.40 (d, $J = 4$ Hz, 1H, 11b-H), 5.06 (t, 1H, 3′-H), 6.88–7.79 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 17.2, 20.6, 21.2, 23.5, 26.0, 28.5, 40.3, 43.2, 49.4, 64.3, 120.2, 122.5, 123.0, 124.2, 124.9, 125.5, 126.8, 127.8, 128.9, 129.5, 130.4, 132.2, 136.7, 142.6, 151.4; ESI-MS (m/z): 445.1 $(M+H)^+$, Anal. Calcd for $C_{28}H_{32}N_2OS$: C, 75.64; H, 7.25; N, 6.30; S, 7.21; Found: C, 75.43; H, 7.46; N, 6.03; S, 6.95.

3-(3-*Chlorophenyl*)-1-*methyl*-5,5*a*,6,11*b*-*tetrahydro*-3*H*-*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**8a**): White solid, yield 88 %, mp 154–156 °C, IR (ν_{max}, cm^{-1}): 3058, 2919, 1599, 1500, 1254, 1067, 1008, 760, 692, 668; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15 (s, 3H, CH_3 of pyrazole), 2.21 (m, 1H, 5a-H), 2.71 (d, $J = 12.8$ Hz, 1H, 5-H), 3.01 (t, $J = 12.4$ Hz, 1H, 5-H), 4.14 (d, $J = 4$ Hz, 1H, 11b-H), 4.23 (d, $J = 11.2$ Hz, 1H, 6′-H), 4.39 (d, $J = 11.2$ Hz, 1H, 6″-H), 6.83–7.66 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.0, 27.5, 31.2, 33.3, 65.7, 113.1, 116.5, 119.3, 120.8, 121.5, 123.3, 127.2, 128.7, 129.7, 131.6, 132.3, 134.6, 139.8, 149.8, 154.1; ESI-MS (m/z): 369.1 $(M+H)^+$, Anal. Calcd for $C_{20}H_{17}ClN_2OS$: C, 65.12; H, 4.65; N, 7.59; S, 8.69; Found: C, 64.97; H, 4.89; N, 7.77; S, 8.41.

3-(3-*Chlorophenyl*)-1,5,5-*trimethyl*-5,5*a*,6,11*b*-*tetrahydro*-3*H*-*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**8b**): White solid, yield 91 %, mp 116–118 °C, IR (ν_{max}, cm^{-1}): 3064, 2965, 2928, 1597, 1488, 1450, 1254, 1031, 1018, 760, 694, 671; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (s, 3H, 5-CH_3), 1.60 (s, 3H, 5-CH_3), 2.13 (s, 3H, CH_3 of pyrazole), 2.18–2.23 (m, 1H, 5a-H), 4.17 (d, $J = 4$ Hz, 1H, 11b-H), 4.19–4.24 (t, $J = 10.8$ Hz, 1H, 6-H), 4.40–4.44 (ddd, $J = 11.2$, $J = 4$, $J = 1.2$ Hz, 1H, 6-H), 6.85–7.64 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.4, 27.2, 30.6, 32.8, 41.4, 45.7, 65.0, 112.2, 116.7, 119.1, 120.9, 121.9, 123.3, 127.0, 128.8, 129.9, 131.5, 132.2, 134.8, 140.4, 149.9, 154.2; ESI-MS (m/z): 397.2 $(M+H)^+$, Anal. Calcd for $C_{22}H_{21}ClN_2OS$: C, 66.57; H, 5.33; N, 7.06; S, 8.08; Found: C, 66.78; H, 5.56; N, 6.78; S, 8.25.

3-(3-*Chlorophenyl*)-1-*methyl*-6, 11*b*-*dihydro*-3*H*-*chromeno*[4′, 3′ : 4, 5]*thiopyrano*[2, 3-*c*]*pyrazole* (**8c**): White solid, yield 86 %, mp 176–178 °C, IR (ν_{max}, cm^{-1}): 3060, 2929, 2850, 1694, 1644, 1601, 1549, 1504, 1290, 1270, 1240, 1218, 1179, 1154, 1101, 1073, 870, 844, 820, 802, 783, 759, 698, 669, 638, 622; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3H, CH_3 of pyrazole), 4.77 (d, $J = 12.4$ Hz, 1H, 6-H), 4.94–4.97 (m, 2H, 6-H & 11b-H), 6.07 (s, 1H, 5-H), 6.83–7.62 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 35.5, 71.8, 109.2, 110.0, 116.8, 119.7, 120.4, 121.3, 123.1, 127.1, 128.7, 129.5, 130.1, 131.2, 132.6, 134.2, 140.2, 149.2, 154.1; ESI-MS (m/z): 367.1 $(M+H)^+$, Anal. Calcd for $C_{20}H_{15}ClN_2OS$: C, 65.48; H, 4.12; N, 7.64; S, 8.74; Found: C, 65.14; H, 4.37; N, 7.35; S, 8.46.

1-*Methyl*-3-(3-*chlorophenyl*)-3,4*a*,5,6,7,7*a*,7*b*,12*b*-*octahydroxantheno*[9′,9*a*′,1′:4,5,6]*thiopyrano*[2,3-*c*]*pyrazole* (**8d**): White solid, yield 89 %, mp 178–180 °C, IR (ν_{max}, cm^{-1}): 3060, 3039, 2962, 2925, 2899, 1611, 1580, 1512, 1451, 1302, 1280, 1230, 1203, 1179, 1150, 1108, 1081, 1070, 868, 849, 821, 783, 764, 733, 699, 651, 628, 612; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52–1.87 (m, 3H, CH_2), 1.93 (s, 3H, CH_3), 1.95–1.99 (m, 1H, CH_2), 2.08–2.13 (m, 1H, 7b-H), 2.21–2.30 (m, 2H, CH_2), 4.04–4.05 (d, 1H, $J = 4$ Hz, 12b-H), 4.10–4.11 (d, 1H, $J = 2.4$ Hz, 4a-H), 4.25–4.33 (m, 1H, 7a-H), 6.84–7.64 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.3, 19.2, 30.1, 32.9, 35.2, 39.7, 41.6, 70.3, 112.0, 116.6, 119.0, 121.0, 121.9, 123.4, 127.2, 128.9, 130.1, 131.7, 132.4, 134.8, 140.5, 149.8, 154.1; ESI-MS (m/z): 409.2 $(M+H)^+$, Anal. Calcd for $C_{23}H_{21}ClN_2OS$: C, 67.55; H, 5.18; N, 6.85; S, 7.84; Found: C, 67.79; H, 5.36; N, 7.08; S, 8.04.

3-(3-*Chlorophenyl*)-1-*methyl*-5-*phenyl*-5,5*a*,6,11*b*-*tetrahydro*-3*H*-*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**8e**): White solid, yield 45 %, mp 255–257 °C, IR (ν_{max}, cm^{-1}): 3057, 3033, 2948, 2921, 2864, 1614, 1588, 1519, 1244, 1207, 1177, 1154, 1099, 1064, 839, 815, 794, 779, 753, 712, 689, 648, 609; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51 (s, 3H, CH_3 of pyrazole), 2.63 (m, 1H, 5a-H), 3.98 (m, 1H, 6-H), 4.27 (m, 1H, 6-H), 4.44 (d, $J = 4$ Hz, 1H, 11b-H), 4.51 (d, $J = 11.2$ Hz, 1H, 5-H), 6.83–7.64 (m, 13H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.5, 33.6, 37.5, 44.1, 67.2, 114.3, 116.3, 120.7, 121.1, 122.4, 123.3, 127.5, 128.6, 128.8, 128.9, 129.7, 129.8, 131.9, 133.4, 135.2, 138.3, 149.8, 152.3; ESI-MS (m/z): 445.1 $(M+H)^+$, Anal. Calcd for $C_{26}H_{21}ClN_2OS$: C, 70.18; H, 4.76; N, 6.30; S, 7.21; Found: C, 70.33; H, 5.05; N, 6.56; S, 6.92.

3-(3-*Chlorophenyl*)-1-*methyl*-5-*phenyl*-5,5*a*,6,11*b*-*tetrahydro*-3*H*-*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**8e′**): White solid, yield 45 %, mp 199–201 °C, IR (ν_{max}, cm^{-1}): 3058, 3029, 2949, 2922, 2861, 1610, 1588, 1519, 1241, 1208, 1180, 1150, 1099, 1060, 839, 815, 794, 777, 751, 712, 689, 648, 610; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H, CH_3 of pyrazole), 2.90 (m, 1H, 5a-H), 3.90 (m, 1H, 6-H), 3.99 (m, 1H, 6-H), 4.04 (d, $J = 10.8$ Hz, 1H, 11b-H), 4.11 (d, $J = 10.8$ Hz, 1H, 5-H), 6.84–7.65 (m, 13H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 37.2, 46.4, 50.6, 71.0, 112.4, 116.5, 120.1, 121.2, 122.5, 124.2, 127.3, 128.2, 128.5, 128.7, 129.3, 129.6, 132.4, 133.1, 135.5, 138.3, 148.7, 154.5; ESI-MS (m/z): 445.1 $(M+H)^+$, Anal. Calcd for $C_{26}H_{21}ClN_2OS$: C, 70.18; H, 4.76; N, 6.30; S, 7.21; Found: C, 70.24; H, 5.01; N, 6.45; S, 6.97.

3-(3-*Chlorophenyl*)-1-*methyl*-5-*phenyl*-5,5*a*-*dihydro*-3*H*-*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazol*-6(11*bH*)-*one* (**8f**): White solid, yield 87 %, mp 236–238 °C, IR (ν_{max}, cm^{-1}): 3010, 2926, 2845, 1766, 1691, 1626, 1541, 1500, 1310, 1278, 1259, 1203, 1174, 1108, 1081, 1074, 869, 839, 770, 738, 714, 698, 649; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H, CH_3 of pyrazole), 3.57 (m, 1H, 5a-H), 4.49 (d, J = 10.4 Hz, 1H, 5-H), 4.53 (d, J = 4 Hz, 1H, 11b-H), 7.11–7.64 (m, 13H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.6, 32.5, 43.4, 46.9, 109.5, 112.3, 117.0, 119.3, 122.7, 124.5, 125.1, 127.5, 128.6, 129.0, 129.0, 129.1, 129.3, 131.4, 132.1, 135.8, 140.3, 148.7, 149.9, 166.5; ESI-MS (m/z): 459.3 $(M+H)^+$, Anal. Calcd for $C_{26}H_{19}ClN_2O_2S$: C, 68.04; H, 4.17; N, 6.10; S, 6.99; Found: C, 68.29; H, 4.37; N, 5.88; S, 7.17.

*Ethyl*3-(3-*chlorophenyl*)-1-*methyl*-5,5*a*,6,11*b*-*tetrahydro*-3*H*-*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole*-5-*carboxylate* (**8g**): Yellow oil, yield 81 %, IR (ν_{max}, cm^{-1}): 3163, 3060, 2971, 2934, 1739, 1670, 1632, 1604, 1548, 1287, 1240, 1170, 1166, 1094, 1058, 1031, 860, 822, 752, 700, 664, 621; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H, 4′-CH_3), 2.51–2.58 (m, 4H, 5a-H & CH_3 of pyrazole), 3.69 (d, J = 11.2 Hz, 1H, 5-H), 4.20–4.25 (m, 2H, Two 3′-H), 4.29–4.32 (m, 1H, 6-H), 4.40 (d, J = 4.4 Hz, 1H, 11b-H), 4.57–4.60 (m, 1H, 6-H), 6.85–7.65 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1, 14.2, 29.3, 36.1, 46.0, 62.6, 65.7, 112.4, 116.7, 119.3, 120.8, 121.7, 123.4, 127.1, 128.7, 128.9, 129.6, 131.4, 132.3, 134.2, 140.2, 151.6, 170.2; ESI-MS (m/z): 441.1 $(M+H)^+$, Anal. Calcd for $C_{23}H_{21}ClN_2O_3S$: C, 62.65; H, 4.80; N, 6.35; S, 7.27; Found: C, 62.67; H, 4.98; N, 6.49; S, 7.52.

3-(3-*Chlorophenyl*)-1,5-*dimethyl*-5-(4-*methylpent*-3-*en*-1-*yl*)-5,5*a*,6,11*b*-*tetrahydro*-3*H*-*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**8h**): Yellow oil, yield 87 %, IR (ν_{max}, cm^{-1}): 3060, 2947, 2923, 2860, 1639, 1610, 1513, 1292, 1250, 1230, 1160, 1084, 812, 740, 674, 662, 611; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H, 5-CH_3), 1.43 (s, 3H, 4′-CH_3), 1.51 (s, 3H, 4′-CH_3), 2.09 (m, 2H, 1′-H & 2′-H), 2.20 (m, 2H, 1′-H & 2′-H), 2.44 (m, 1H, 5a-H), 2.53 (s, 3H, CH_3 of pyrazole), 4.02 (t, 1H, 6-H), 4.15 (m, 1H, 6-H), 4.38 (d, J = 4 Hz, 1H, 11b-H), 5.07 (t, 1H, 3′-H), 6.87–7.77 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 17.7, 21.2, 22.4, 25.6, 27.2, 39.4, 43.3, 49.6, 64.9, 112.4, 116.5, 119.2, 120.8, 121.7, 123.3, 124.3, 124.9, 127.1, 128.8, 129.7, 131.4, 132.2, 134.7, 140.5, 149.7, 154.3; ESI-MS (m/z): 465.1 $(M+H)^+$, Anal. Calcd for $C_{27}H_{29}ClN_2OS$: C, 69.73; H, 6.29; N, 6.02; S, 6.89; Found: C, 70.04; H, 6.53; N, 6.24; S, 7.12.

13-(3-*Chlorophenyl*)-11-*methyl*-2*a*,3,10*c*,13-*tetrahydro*-2*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**9a**): White solid, yield 89 %, mp 178–180 °C, IR (ν_{max}, cm_{-1}): 3055, 2984, 2930, 2901, 1599, 1515, 1500, 1229, 1025, 1013, 832, 764, 743, 691, 674; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H, CH_3 of pyrazole), 2.92 (m, 2H, 2-H and 2a-H), 3.59 (dd, J = 12, J = 4 Hz, 1H, 2′-H), 4.21 (d, J = 8 Hz, 2H, Two 3-H), 4.63 (d, J = 3.2 Hz, 1H, 10c-H), 7.11–7.99 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 29.5, 30.8, 31.7, 65.5, 112.4, 114.5, 118.8, 121.0, 122.6, 123.3, 123.4, 126.6, 127.0, 128.6, 128.9, 129.2, 130.0, 131.8, 133.7, 134.7, 140.6, 149.8, 151.8; ESI-MS (m/z): 419.1 $(M+H)^+$, Anal. Calcd for $C_{24}H_{19}ClN_2OS$: C, 68.81; H, 4.57; N, 6.69; S, 7.65; Found: C, 69.08; H, 4.74; N, 6.88; S, 7.39.

13-(3-*Chlorophenyl*)-2,2,11-*trimethyl*-2*a*,3,10*c*,13-*tetrahydro*-2*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**9b**): White solid, yield 91 %, mp 232–234 °C, IR (ν_{max}, cm^{-1}): 3064, 2963, 2917, 1621, 1593, 1516, 1231, 1134, 1015, 831, 818, 781, 748, 686, 663, 603; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 3H, 2-CH_3), 1.55 (s, 3H, 2-CH_3), 1.75 (s, 3H, CH_3 of pyrazole), 2.22–2.27 (m, 1H, 2a-H), 4.22 (t, J = 11.2 Hz, 1H, 3-H), 4.45–4.49 (dd, J = 10.8 HZ, J = 3.6, 1H, 3-H), 4.83 (d, J = 3.2 HZ, 1H, 10c-H), 7.09–8.10 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 27.3, 27.5, 32.1, 41.6, 45.8, 64.6, 112.5, 114.5, 118.8, 121.0, 122.3, 123.2, 123.4, 126.5, 127.0, 128.6, 128.9, 129.2, 130.0, 131.7, 133.6, 134.8, 140.6, 149.8, 151.8; ESI-MS (m/z): 447.2 $(M+H)^+$, Anal. Calcd for $C_{26}H_{23}ClN_2OS$: C, 69.86; H, 5.19; N, 6.27; S, 7.17; Found: C, 70.07; H, 5.38; N, 6.42; S, 7.22.

13-(3-*Chlorophenyl*)-11-*methyl*-10*c*,13-*dihydro*-3*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**9c**):White solid, yield 86 %, mp 218–220 °C, IR (ν_{max}, cm^{-1}): 3054, 2920, 2848, 1703, 1654, 1581, 1554, 1510, 1294, 1266, 1234, 1202, 1184, 1149, 1118, 1069, 864, 847, 821, 810, 780, 754, 690, 657, 628, 611; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 3H, CH_3 of pyrazole), 4.72 (d, J = 12.4 Hz, 1H, 3-H), 4.92 (m, 2H, 3-H & 10c-H), 6.02 (s, 1H, 2-H), 7.06–8.23 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 35.2, 72.5, 106.4, 115.5, 121.1, 122.6, 123.4, 124.6, 124.8, 127.1, 127.5, 129.7, 130.1, 131.2, 132.3, 133.7, 134.8, 136.3, 140.4, 141.7, 143.7, 149.8, 151.3; ESI-MS (m/z): 417.2 $(M+H)^+$, Anal. Calcd for $C_{24}H_{17}ClN_2OS$: C, 69.14; H, 4.11; N, 6.72; S, 7.69; Found: C, 69.31; H, 4.25; N, 7.05; S, 7.86.

1-*Methyl*-3-(3-*chlorophenyl*)-3,4*a*,5,6,7,7*a*,7*b*,14*c*-*octahydrobenzo*[7′,8′]*xantheno*[9′,9*a*′,1′:4,5,6]*thiopyrano*[2,3-*c*]*pyrazole* (**9d**): White solid, yield 88 %, mp 194–196 °C, IR (ν_{max}, cm^{-1}): 3039, 3005, 2920, 2877, 1613, 1511, 1444, 1312, 1269, 1248, 1199, 1166, 1140, 1100, 1083, 1060, 860, 839, 820, 780, 755, 721, 694, 648, 630, 613; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04–1.70 (m, 4H, CH_2), 1.73 (s, 3H, CH_3 of pyrazole), 1.74–1.87 (m, 2H, CH_2), 2.34 (m, 1H, 7b-H), 3.47 (m, 1H, 4a-H), 4.39 (m, 1H, 7a-H), 4.70 (d, 1H, J = 4 Hz, 14c-H), 7.11–7.90 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 20.3, 27.2, 29.7, 31.0, 42.1, 48.3, 75.0, 113.3, 119.1, 121.1, 121.7, 122.1, 123.2, 126.3, 127.0, 128.7, 129.5, 130.0, 133.1, 134.7, 135.5, 136.5, 140.6, 146.1, 149.7, 152.2; ESI-MS (m/z): 459.1 $(M+H)^+$, Anal. Calcd for $C_{27}H_{23}ClN_2OS$: C, 70.65; H, 5.05; N, 6.10; S, 6.99; Found: C, 70.84; H, 5.27; N, 6.27; S, 7.19.

13-(3-*Chlorophenyl*)-11-*methyl*-2-*phenyl*-2*a*,3,10*c*,13-*tetrahydro*-2*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**9e**): White solid, yield 89 %, mp 226–228 °C, IR (ν_{max}, cm^{-1}): 3055, 2924, 2862, 1651, 1621, 1599, 1518, 1283, 1260, 1234, 1177, 1164, 1141, 1090, 866, 823, 771, 752, 731, 699, 666, 611; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 3H, CH_3 of pyrazole), 3.05 (m, 1H, 2a-H), 3.95 (d, J = 5.6 Hz, 1H, 2-H), 4.00 (t, 1H, 3-H), 4.22 (m, 1H, 3-H), 4.63 (d, J = 4 Hz, 1H, 10c-H), 7.10–7.88 (m, 15H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1, 30.3, 43.2, 50.3, 66.1, 113.1, 116.9, 118.8, 121.1, 122.6, 123.5, 126.8, 127.1, 128.0, 128.2, 128.6, 128.8, 128.9, 129.7, 130.0, 131.9, 133.8, 134.7, 136.8, 136.9, 140.4, 149.7, 151.8; ESI-MS (m/z): 495.2 $(M+H)^+$, Anal. Calcd for $C_{30}H_{23}ClN_2OS$: C, 72.79; H, 4.68; N, 5.66; S, 6.48; Found: C, 73.04; H, 4.84; N, 5.87; S, 6.71.

13-(3-*Chlorophenyl*)-11-*methyl*-2-*phenyl*-10*c*,13-*dihydro*-2*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazol*-3(2*aH*)-*one* (**9f**): White solid, yield 85 %, mp 202–204 °C, IR (ν_{max}, cm^{-1}): 3020, 2930, 2835, 1760, 1689, 1631, 1537, 1511, 1317, 1266, 1250, 1188, 1169, 1111, 1081, 1061, 864, 844, 772, 748, 701, 690, 640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 3H, CH_3 of pyrazole), 3.03 (m, 1H, 2a-H), 3.91 (d, J = 5.6 Hz, 1H, 2-H), 4.63 (d, J = 4.4 HZ, 1H, 10c-H), 7.08–7.92 (m, 15H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3, 30.2, 43.1, 50.4, 117.4, 120.1, 121.6, 122.5, 124.9, 126.9, 127.1, 127.4, 127.7, 128.8, 129.0, 129.4, 130.1, 132.7, 134.8, 136.6, 136.8, 136.9, 139.1, 140.7, 142.7, 150.9, 166.6; ESI-MS (m/z): 509.1 $(M+H)^+$, Anal. Calcd for $C_{30}H_{21}ClN_2O_2S$: C, 70.79; H, 4.16; N, 5.50; S, 6.30; Found: C, 71.03; H, 4.34; N, 5.74; S, 6.52.

*Ethyl*13-(3-*chlorophenyl*)-11-*methyl*-2*a*,3,10*c*,13-*tetrahydro*-2*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*-[2,3-*c*]*pyrazole*-2-*carboxylate* (**9g**): Yellow oil, yield 82 %, IR (ν_{max}, cm^{-1}): 3160, 3055, 2980, 2928, 1732, 1670, 1624, 1599, 1515, 1299, 1231, 1177, 1161, 1094, 1062, 1024, 864, 819, 752, 712, 666, 615; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H, 4′-CH_3), 1.37 (s, 3H, CH_3 of pyrazole), 3.16 (m, 1H, 2a-H), 3.69 (d, J = 4.4 HZ, 1H, 2-H), 3.98 (t, 1H, 3-H), 4.25 (m, 3H, 3-H & Two 3′-H), 4.80 (d, J = 5.2 Hz, 1H, 10c-H), 7.11–7.97 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2, 14.2, 29.1, 36.3, 46.1, 62.5, 65.7, 113.3, 115.5, 118.7, 121.1, 122.4, 123.5, 126.9, 127.2, 128.6, 129.2, 129.4, 129.6, 130.2, 133.8, 134.7, 136.6, 137.2, 148.6, 151.5, 170.2; ESI-MS (m/z): 491.2 $(M+H)^+$, Anal. Calcd for $C_{27}H_{23}ClN_2O_3S$: C, 66.05; H, 4.72; N, 5.71; S, 6.53; Found: C, 66.27; H, 4.53; N, 5.54; S, 6.78.

13-(3-*Chlorophenyl*)-2,11-*dimethyl*-2-(4-*methylpent*-3-*en*-1-*yl*)-2*a*,3,10*c*,13-*tetrahydro*-2*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**9h**): Yellow oil, yield 87 %, IR (ν_{max}, cm^{-1}): 3066, 2954, 2926, 2859, 1626, 1605, 1523, 1299, 1258, 1236, 1164, 1092, 822, 753, 699, 664, 619; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 3H, 2-CH_3), 1.46 (s, 3H, 4′-CH_3), 1.52 (s, 3H, 4′-CH_3), 1.71 (s, 3H, CH_3 of pyrazole), 2.03–2.07 (m, 2H, 2′-H & 1′-H), 2.19–2.23 (m, 2H, 2a-H & 1′-H), 2.41 (s, 1H, 2′-H), 4.35 (t, 1H, 3-H), 4.50 (m, 1H, 3-H), 4.89 (d, J = 4.8 Hz, 1H, 10c-H), 5.17 (t, 1H, 3′-H), 7.11–8.11 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 17.6, 22.1, 23.6, 25.7, 27.0, 39.9, 43.2, 49.0, 64.8, 111.8, 114.6, 118.7, 121.2, 122.5, 123.2, 123.2, 123.5, 126.5, 127.0, 128.6, 128.8, 129.5, 130.4, 131.5, 132.4, 133.6, 134.7, 137.2, 148.8, 151.7; ESI-MS (m/z): 515.2 $(M+H)^+$, Anal. Calcd for $C_{31}H_{31}ClN_2OS$: C, 72.28; H, 6.07; N, 5.44; S, 6.22; Found: C, 72.46; H, 6.32; N, 5.70; S, 6.48.

11-*Methyl*-13-*phenyl*-2*a*,3,10*c*,13-*tetrahydro*-2*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**10a**): White solid, yield 90 %, mp 171–173 °C, IR (ν_{max}, cm^{-1}): 3058, 2929, 2901, 1598, 1517, 1499, 1226, 1027, 1011, 813, 760, 741, 695, 670; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H, CH_3 of pyrazole), 2.87–2.94 (m, 2H, 2-H and 2a-H), 3.57–3.61 (dd, J = 12, J = 4 Hz, 1H, 2-H), 4.20–4.22 (m, 2H, Two 3-H), 4.64 (d, J = 3.2 Hz, 1H, 10c-H), 7.11–7.99 (m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 30.6, 30.9, 31.7, 65.4, 114.2, 114.9, 115.5, 118.7, 119.2, 120.7, 122.4, 123.1, 126.7, 127.1, 128.6, 129.1, 130.3, 130.5, 133.7, 139.4, 151.6; ESI-MS (m/z): 385.2 $(M+H)^+$, Anal. Calcd for $C_{24}H_{20}N_2OS$: C, 74.97; H, 5.24; N, 7.29; S, 8.34; Found: C, 74.68; H, 5.44; N, 7.56; S, 8.59.

2,2,11-*Trimethyl*-13-*phenyl*-2*a*,3,10*c*,13-*tetrahydro*-2*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* (**10b**): White solid, yield 89 %, mp 198–200 °C, IR (ν_{max}, cm^{-1}): 3058, 2985, 2959, 2927, 1626, 1599, 1525, 1230, 1138, 1020, 999, 820, 755, 696, 660; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 3H, 2-CH_3), 1.54 (s, 3H, 2-CH_3), 1.74 (s, 3H, CH_3 of pyrazole), 2.23 (td, J = 11.6, J = 4.4 Hz, 1H, 2a-H), 4.26 (t, J = 11.2 Hz, 1H, 3-

H), 4.47 (ddd, J = 12 HZ, J = 5.6, J = 2.4, 1H, 3-H), 4.85 (d, J = 3.6 HZ, 1H, 10c-H), 7.11–8.13 (m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 27.3, 27.6, 32.1, 41.6, 45.5, 64.6, 112.0, 114.6, 118.8, 122.5, 123.2, 123.4, 126.5, 127.1, 128.6, 128.8, 129.0, 129.1, 131.5, 133.7, 139.5, 149.3, 151.8; ESI-MS (m/z): 413.2 $(M+H)^+$, Anal. Calcd for $C_{26}H_{24}N_2OS$: C, 75.70; H, 5.86; N, 6.79; S, 7.77; Found: C, 75.56; H, 6.12; N, 6.57; S, 8.06.

11-*Methyl*-13-*phenyl*-10*c*,13-*dihydro*-3*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* **(10c)**: White solid, yield 85 %, mp 206–208 °C, IR (ν_{max}, cm^{-1}): 3059, 2927, 2842, 1708, 1650, 1588, 1557, 1516, 1299, 1266, 1237, 1201, 1186, 1149, 1118, 1066, 865, 848, 822, 816, 777, 750, 694, 660, 629, 617; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 3H, CH_3 of pyrazole), 4.74 (d, J = 12.4 Hz, 1H, 3-H), 4.92 (m, 2H, 3-H & 10c-H), 6.02 (s, 1H, 2-H), 7.08–8.23 (m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 35.3, 72.5, 106.3, 115.5, 119.2, 122.6, 123.4, 124.8, 127.2, 127.5, 129.7, 130.2, 130.5, 131.2, 132.3, 133.6, 136.4, 139.6, 141.8, 143.8, 151.4; ESI-MS (m/z): 383.1 $(M+H)^+$, Anal. Calcd for $C_{24}H_{18}N_2OS$: C, 75.37; H, 4.74; N, 7.32; S, 8.38; Found: C, 75.64; H, 4.46; N, 7.56; S, 8.51.

1-*Methyl*-3-*phenyl*-3,4*a*,5,6,7,7*a*,7*b*,14*c*-*octahydrobenzo*[7′,8′]*xantheno*[9′,9*a*′,1′:4,5,6]*thiopyrano*[2,3-*c*]*pyrazole* **(10d)**: White solid, yield 90 %, mp 184–186 °C, IR (ν_{max}, cm^{-1}): 3033, 3002, 2920, 2879, 1610, 1516, 1444, 1310, 1266, 1248, 1199, 1168, 1140, 1100, 1077, 1059, 858, 834, 824, 783, 762, 725, 696, 648, 639, 615; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01–1.70 (m, 4H, CH_2), 1.73 (s, 3H, CH_3 of pyrazole), 1.75–1.86 (m, 2H, CH_2), 3.22 (m, 1H, 7b-H), 3.48 (m, 1H, 4a-H), 4.39 (m, 1H, 7a-H), 4.70 (d, 1H, J = 4 Hz, 14c-H), 7.11–7.90 (m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.8, 20.2, 27.2, 29.7, 31.0, 42.1, 48.3, 74.9, 113.3, 115.5, 120.7, 121.7, 122.1, 123.0, 126.3, 127.1, 128.7, 129.4, 130.8, 133.5, 135.6, 136.6, 139.3, 146.2, 152.1; ESI-MS (m/z): 425.1 $(M+H)^+$, Anal. Calcd for $C_{27}H_{24}N_2OS$: C, 76.38; H, 5.70; N, 6.60; S, 7.55; Found: C, 76.49; H, 5.58; N, 6.46; S, 7.34.

11-*Methyl*-2,13-*diphenyl*-2*a*,3,10*c*,13-*tetrahydro*-2*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* **(10e)**: White solid, yield 88 %, mp 216–218 °C, IR (ν_{max}, cm^{-1}): 3063, 2925, 2868, 1655, 1623, 1599, 1512, 1285, 1260, 1236, 1177, 1166, 1147, 1093, 866, 823, 770, 756, 733, 699, 670, 616; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 3H, CH_3 of pyrazole), 3.04 (m, 1H, 2a-H), 3.95 (d, J = 5.6 Hz, 1H, 2-H), 4.02 (t, 1H, 3-H), 4.24 (m, 1H, 3-H), 4.61 (d, J = 4 Hz, 1H, 10c-H), 7.10–7.87 (m, 16H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1, 29.9, 43.1, 50.2, 66.0, 113.2, 115.5, 116.9, 118.6, 119.3, 120.6, 122.4, 123.5, 126.6, 127.3, 128.2, 128.6, 128.7, 128.9, 130.4, 131.8, 133.4, 136.9, 140.4, 148.6, 151.8; ESI-MS (m/z): 461.2 $(M+H)^+$, Anal. Calcd for $C_{30}H_{24}N_2OS$: C, 78.23; H, 5.25; N, 6.08; S, 6.96; Found: C, 78.46; H, 5.37; N, 5.87; S, 6.76.

11-*Methyl*-2,13-*diphenyl*-10*c*,13-*dihydro*-2*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazol*-3(2*aH*)-*one* **(10f)**: White solid, yield 86 %, mp 196–198 °C, IR (ν_{max}, cm^{-1}): 3028, 2934, 2832, 1764, 1688, 1631, 1539, 1511, 1321, 1268, 1253, 1188, 1166, 1116, 1087, 1068, 864, 840, 777, 751, 702, 697, 641; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 3H, CH_3 of pyrazole), 3.03 (m, 1H, 2a-H), 3.94 (d, J = 5.6 Hz, 1H, 2-H), 4.62 (d, J = 4 HZ, 1H, 10c-H), 7.06–7.91 (m, 16H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1, 30.1, 43.0, 50.3, 115.6, 117.5, 120.7, 121.5, 122.6, 123.4, 124.9, 126.8, 127.5, 127.6, 127.7, 128.8, 129.3, 130.2, 132.7, 134.6, 136.6, 139.1, 142.7, 150.9, 166.6; ESI-MS (m/z): 475.1 $(M+H)^+$, Anal. Calcd for $C_{30}H_{22}N_2O_2S$: C, 75.93; H, 4.67; N, 5.90; S, 6.76; Found: C, 75.67; H, 4.46; N, 4.87; S, 6.57.

*Ethyl*11-*methyl*-13-*phenyl*-2*a*,3,10*c*,13-*tetrahydro*-2*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole*-2-*carboxylate* **(10g)**: Yellow oil, yield 84 %, IR (ν_{max}, cm^{-1}): 3166, 3062, 2982, 2933, 1737, 1678, 1620, 1601, 1512, 1299, 1235, 1179, 1162, 1097, 1065, 1022, 860, 823, 751, 711, 668, 614; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H, 4′-CH_3), 1.37 (s, 3H, CH_3 of pyrazole), 3.16 (m, 1H, 2a-H), 3.71 (d, J = 4 HZ, 1H, 2-H), 4.01 (t, 1H, 3-H), 4.25 (m, 3H, 3-H & Two 3′-H), 4.82 (d, J = 5.2 Hz, 1H, 10c-H), 7.11–7.97 (m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1, 14.1, 29.1, 36.3, 46.0, 62.4, 65.7, 113.3, 115.5, 118.6, 120.4, 122.6, 123.5, 126.8, 127.3, 128.6, 129.7, 130.6, 133.8, 136.5, 137.2, 139.7, 148.6, 151.5, 170.2; ESI-MS (m/z): 457.2 $(M+H)^+$, Anal. Calcd for $C_{27}H_{24}N_2O_3S$: C, 71.03; H, 5.30; N, 6.14; S, 7.02; Found: C, 71.31; H, 5.57; N, 6.42; S, 7.29.

2,11-*Dimethyl*-2-(4-*methylpent*-3-*en*-1-*yl*)-13-*phenyl*-2*a*,3,10*c*,13-*tetrahydro*-2*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole* **(10h)**: Yellow oil, yield 85 %, IR (ν_{max}, cm^{-1}): 3065, 2963, 2927, 2855, 1628, 1603, 1520, 1297, 1258, 1236, 1162, 1089, 822, 749, 699, 661, 618; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 3H, 2-CH_3), 1.45 (s, 3H, 4′-CH_3), 1.50 (s, 3H, 4′-CH_3), 1.72 (s, 3H, CH_3 of pyrazole), 2.06 (m, 2H, 2′-H & 1′-H), 2.22 (m, 2H, 2a-H & 1′-H), 2.40 (s, 1H, 2′-H), 4.34 (t, 1H, 3-H), 4.51 (m, 1H, 3-H), 4.88 (d, J = 2.8 Hz, 1H, 10c-H), 5.16 (t, 1H, 3′-H), 7.10–8.11 (m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 17.7, 22.0, 23.6, 25.6, 27.0, 39.9, 43.1, 49.0, 64.7, 111.9, 114.6, 115.5, 118.8, 120.7, 122.4, 123.2, 126.5, 127.3, 128.6, 129.1, 129.6, 130.4, 131.6, 132.5, 133.7, 139.4, 148.9, 151.8; ESI-MS (m/z): 481.2 $(M+H)^+$, Anal. Calcd for $C_{31}H_{32}N_2OS$: C, 77.46; H, 6.71; N, 5.83; S, 6.67; Found: C, 77.65; H, 6.64; N, 5.67; S, 6.48.

2,2,11-*Trimethyl*-13-*phenyl*-2*a*,3,10*c*,13-*tetrahydro*-2*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole*1-*oxide* **(11)**: White solid, mp 208–209 °C, IR (ν_{max}, cm^{-1}): 3063, 2970, 2932, 2862, 1744, 1605, 1497, 1304, 1234, 1088, 1041, 818, 764, 694, 687; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (s, 3H, 2-CH_3), 1.60 (s, 3H, 2-CH_3), 1.74 (s, 3H, CH_3 of pyrazole), 2.57 (td, $J = 12$, $J = 4$ Hz, 1H, 2a-H), 4.56 (m, 1H, 3-H), 4.84 (d, $J = 2.8$, 1H, 10c-H), 4.91 (t, 1H, 3-H), 7.12–8.01 (m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 21.9, 23.1, 28.7, 42.3, 54.5, 63.1, 112.0, 117.0, 119.0, 120.3, 122.3, 123.3, 125.2, 126.6, 128.6, 129.0, 129.4, 129.7, 133.7, 136.5, 138.7, 148.3, 152.1; ESI-MS (m/z): 429.4 $(M+H)^+$, Anal. Calcd for $C_{26}H_{24}N_2O_2S$: C, 72.87; H, 5.64; N, 6.54; S, 7.48; Found: C, 72.64; H, 5.83; N, 6.79; S, 7.27.

2,2,11-*Trimethyl*-13-*phenyl*-2*a*,3,10*c*,13-*tetrahydro*-2*H*-*benzo*[5′,6′]*chromeno*[4′,3′:4,5]*thiopyrano*[2,3-*c*]*pyrazole*-1,1-*dioxide* **(12)**: White solid, mp 194–196 °C, IR (ν_{max}, cm^{-1}): 3063, 2970, 2932, 1744, 1736, 1620, 1597, 1381, 1288, 1234, 1157, 1119, 1026, 764, 694, 648; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (s, 3H, 2-CH_3), 1.62 (s, 3H, 2-CH_3), 1.84 (s, 3H, CH_3 of pyrazole), 2.61 (m, 1H, 2a-H), 4.57 (m, 2H, Two 3-H), 5.05 (d, $J = 2.8$ Hz, 1H, 10c-H), 7.12–7.99 (m, 11H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 18.1, 24.1, 27.8, 46.4, 60.8, 63.4, 111.8, 118.9, 120.5, 122.1, 123.6, 125.5, 126.9, 128.6, 128.9, 129.0, 129.1, 130.0, 133.5, 134.0, 139.1, 148.0, 151.9; ESI-MS (m/z): 445.4 $(M+H)^+$, Anal. Calcd for $C_{26}H_{24}N_2O_3S$: C, 70.25; H, 5.44; N, 6.30; S, 7.21; Found: C, 70.48; H, 5.15; N, 6.51; S, 7.46.

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