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Graphical Abstract

Synthesis of Novel Benzo[4,5]thiazolo[1,2-*a*]pyrimidine-3-carboxylate Derivatives and Biological Evaluation as Potential Anticancer Agents

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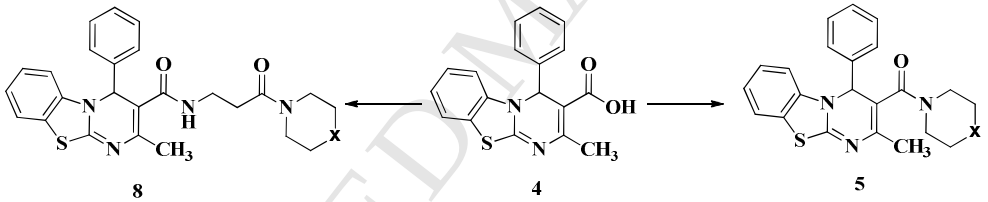
Lingaiah Nagarapu[a]*, Satheeshvarma Vanaparthi[a], Rajashaker Bantu[a], Ganesh Kumar C[b]

A novel series of building blocks consisting of benzo[4,5]thiazolo[1,2-*a*]pyrimidine-3-carboxylate as potential tumor growth inhibitors were synthesized and screened for their cytotoxicity against the human cancer cell lines *in vitro*.



Synthesis of Novel Benzo[4,5]thiazolo[1,2-*a*]pyrimidine-3-carboxylate Derivatives and Biological Evaluation as Potential Anticancer Agents

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ABSTRACT

A novel series of building blocks consisting of benzo[4,5]thiazolo[1,2-*a*]pyrimidine-3-carboxylate have been synthesized as potential anticancer compounds. These compounds were prepared from 2-aminobenzothiazole, benzaldehyde and ethyl acetoacetate in ethylene glycol by catalyzing with TBAHS to give benzo[4,5]thiazo[1,2-*a*]pyrimidine derivative **4** followed by the formation of amide by reaction with several secondary amines in good yields. The cytotoxicity of these compounds was evaluated against human cancer cell lines *in vitro* (A549, HeLa, MDA-MB-231 and MCF-7). Compound **5b** exhibited promising cytotoxicity with IC_{50} values of 0.58 and 1.58 μM specifically against human breast adenocarcinoma cell lines, MCF-7 and MDA-MB-231, while compound **5a** showed promising cytotoxicity against MDA-MB-231 (IC_{50} value of 5.01 μM).

Keywords: Pyrimidine-3-carboxylate, Cytotoxicity, Growth inhibition, Lung Carcinoma A549 cell line, Human breast adenocarcinoma cell.

1. Introduction

The treatment of tumour therapy remains an important and challenging therapeutic problem; the majority of the solid tumours are currently not curable by chemotherapy. Half of all cancer patients fail to respond to chemotherapy or relapse from the initial response and ultimately die from their metastatic disease [1]. The discovery and development of new, more active, more selective, and less toxic compounds for the treatment of malignancy are one of the most important goals in medicinal chemistry. In recent years, interest in the

development of new anticancer drugs increased mainly from emerging resistance against drugs. The development of potential drugs has efficiently improved therapeutic index and tumour growth inhibition. The aim of most cancer chemotherapeutic drugs currently in clinical use is to kill malignant tumour cells by inhibiting some of the mechanisms implied in cellular division. Early approaches of selectively inhibit tumour growth were generally disappointing in clinical studies. The investigation of tumour growth inhibitors is a major obstacle in the medical field [2]. For these reasons, the developments of novel antitumour drugs and their derivatives is still necessary and have very much demand.

Pyrimidines have a long distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of AIDS. The pyrimidine ring is found in vitamins like thiamine, riboflavin and folic acid. During the last two decades, several pyrimidine derivatives have been developed as chemotherapeutic agents and have found wide clinical applications. Benzothiazoles represent a class of heterocyclic compounds of great importance in biological chemistry. They exist in many condensed fused systems that were found to possess a wide range of activity [3-5]. Various literature reports display numerous fused pyrimidine ring systems and their chemotherapeutic activities as anticancer [6-8], antibacterial [9] and antiviral [10] agents. Since the two heterocyclic moieties, benzothiazoles and pyrimidines, constitute two active pharmacophores that are highly active against antitumour and antimicrobial, combining the two is expected to have a synergistic effect on their biological properties. Also substituted thiazolopyrimidine ring systems were reported to possess antitumour activity [11]. The reported significance of such synthons generated the interest to exploit this valuable structure in the designing and the synthesis of new benzo[4,5]thiazolo[1,2-*a*]pyrimidine-3-carboxylate derivatives.

Our on-going research programme [12-16], is to discover and develop tumour growth inhibitors and apoptosis inducers as potential new anti cancer agents, we obtained designed and synthesized novel benzo[4,5]thiazolo[1,2-*a*]pyrimidine-3-carboxylate derivatives which has antitumour activity. Analysis of structure-activity relationships identified the benzothiazole and pyrimidines nucleus as being essential for potent activity, and substitution at the carboxylic acid 3'-position of the benzothiazopyrimidine ring when condensed with methyl piperazine and piperidine moieties increases the cytotoxicity activity

against human breast cancer cell lines MDA-MB-231 and MCF-7 more efficiently, when compare to the secondary amines which shows moderate activity with the above cell line in *vitro*. When chain length was increased with the condensation of *β*-alanine at the third position of benzothiazopyrimidine ring, decreases the cytotoxicity compare to piperidine and methylpiperazine moieties **5a** and **5b**. Significantly, (2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-3-yl)(piperidine-1-yl) methanone (**5a**), and (2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-3-yl)(4-methylpiperazin-1-yl)methanone (**5b**) outperformed their best cytotoxicity activity against breast cancer cell lines in the IC_{50} range of 0.58-5.08 µM.

2. Results and discussion

2.1 *Chemistry*

2.1 *Synthesis of* [4,5]thiazo[1,2-*a*]pyrimidine

The key intermediate used for the synthesis of final compounds of both the series was 2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylic acid **4**, which in turn was prepared by one-pot condensation of 2-aminobenzothiazole (**1**) with substituted benzaldehyde (**2**) and ethyl acetoacetate (**3**) in the presence of ethylene glycol by catalyzing with TBAHS to give crude compound which was hydrolyzed using KOH, ethanol refluxed to get the targeted compound, 2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylic acid (**4**), in quantitative yield (80%) (Scheme 1). Formation of compound **4** was confirmed by the presence of C=N stretching at 1542 and C-S-C stretching band at 1254 cm^{-1} in IR spectrum.

<<< Scheme 1. >>>

Treatment of pyrimidine-3-carboxylic acid **4** with 2^{o}-amines in the presence of HOBt, EDC.HCl and triethylamine at room temperature gave the (2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-3-yl)(piperidin-1-yl)methanone derivatives (**5a-e**) in good to excellent yields (Scheme 2). Structure of **5a** was elucidated on the basis of stretching band at 1634 cm^{-1} of C=O.

In another reaction, ethyl-3-(2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxamido)propanoate (**6**) was obtained in good yield by the condensation of pyrimidine-3-carboxylic acid (**4**) with *β*-alanine ethyl ester in the presence of HOBt, EDC.HCl and triethylamine and the compound **6** was confirmed based on appearance of

bands at 1642, 1623 cm^{-1} for C=O and ester carbonyl stretching in IR spectrum. The ^1H NMR spectra showed the characteristic ester signals at δ 1.22 as triplet representing three hydrogens and δ 3.42-3.52 as a multiplet representing for two protons of ester $–CH_2$. Upon hydrolyzing the compound **6** was converted to 3-(2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxamido)propanoic acid (**7**) using KOH, ethanol at reflux temperature. Treatment of compound **7** with piperidine in the presence of HOBt, EDC.HCl and triethylamine at room temperature gave the targeted methyl-*N*-(3-oxo-3-(piperidin-1-yl)propyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxamide (**8a**) in good yield. The formation of the compound **8a** was evident from mass spectrum [ES+] by the appearance of molecular ion peak at m/z 461, IR spectrum shows bands at 1613 and 1632 cm^{-1} which are attributed to C=O stretching, ^1H NMR by the appearance of piperidine protons at δ 1.41-1.71 as a multiplet representing for six protons and δ 3.38-3.57 as multiplet representing for four protons. The synthetic strategy to prepare the targeted compounds **5a-e** and **8a-e** is illustrated in Scheme 2 and 3.

<<< Scheme 2. >>>

<<< Scheme 3. >>>

In our studies we have planned to synthesize a new analogues of benzo[4,5]thiazo[1,2-*a*]pyrimidine through a one pot-three component reaction of 2-aminobenzothiazole, benzaldehyde and ethyl acetoacetate in ethylene glycol by catalyzing with TBAHS to give benzo[4,5]thiazo[1,2-*a*]pyrimidine derivative which was hydrolyzed by using KOH, ethanol at reflux conditions to give corresponding carboxylic acid **4.** The required benzothiazopyrimidine derivatives **5a-e** was achieved by the reaction between carboxylic acid **4** and a variety of 2^o-amines. In the next step, acid **4** was also reacted with *β*-alanine ethyl ester to give the corresponding ester **6**. The ester was hydrolyzed with KOH, ethanol reflux to give corresponding acid **7,** which subsequently reacted with 2^o-amine to give the desired product **8**. Here we have to study the structure-activity relationship between these two types of compounds. The synthesized compounds were evaluated for anti-cancer activity against different human cancer cell lines *in vitro.*

2.2 *Effects of the compounds on the viability of human cancer cells*

The newly synthesized benzo[4,5]thiazolo[1,2-*a*]pyrimidine-3-carboxylate derivatives (**5a-e**) were further evaluated for their *in vitro* cytotoxicity against breast adenocarcinoma (MDA-MB-231, MCF-7), cervical cancer (HeLa), and alveolar adenocarcinoma (A549) cell lines using the standard MTT assay[17]. From the data reported in Table 1, most of the prepared compounds possessed good cytotoxicity effect on all the tested cell lines and potencies of some compounds were comparable to the standard doxorubicin. The compounds **5a, 5b** and **5c** showed promising inhibitory activity against human breast adenocarcinoma cell lines, MCF-7 and MDA-MB-231, with IC_{50} values ranging from 0.58 µM-11.74 µM, while compounds **5d** and **5e** showed moderate inhibitory activities. Compounds **8a** and **8e** exhibited good cytotoxicity against all the tested cell lines with IC_{50} values ranging from 11.18 µM-25.69 µM.

It has been observed from activity Table 1, that the compound with methyl piperazine and piperidine moieties attached to 2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylic acid are showed higher cytotoxicity as compared with other 2^{o} amines. For example, compound **5b** bearing methyl piperazine moiety showed most potent cytotoxicity in human breast adenocarcinoma cell lines MDA-MB-231 and MCF-7with the IC_{50} values 1.58 µM and 0.58µ M. The compound **5a** bearing piperidine moiety showed most potent cytotoxicity in human breast adenocarcinoma cell line MDA-MB-231 with the IC_{50} value 5.01µM. The compounds **5c-5e** is showing moderate potent cytotoxicity against human breast adenocarcinoma cell lines. The compounds **8a** and **8e** showed moderate cytotoxicity against four cancer cell lines HeLa, MDA-MB-231, MCF-7, and A549 which are Human cervical cancer cell line, Human breast adenocarcinoma cell line, and Human alveolar adenocarcinoma cell line respectively. The results indicated that the attachment of methyl piperazine and piperidine ring with the basic moiety of 2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylic acid (**4**) facilitated the increase of their antitumour activity.

<<<<<<Table 1>>>>>>

3. Conclusion

In conclusion, various substituted (2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-3-yl)(piperidin-1-yl)methanone derivatives (**5a-e**) and 2-methyl-*N*-(3-oxo-3-

(piperidin-1-yl)propyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxamide (**8a-e**) have been prepared from 2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylic acid (**4**) and screened for *in vitro* cytotoxicity activity against A549, HeLa, MDA-MB-231 and MCF-7 cell lines. In general, most compounds showed significant cytotoxicity effect against human breast adenocarcinoma MDA-MB-231 and MCF-7 tumour cell lines, altogether compounds **5a** and **5b** are effective in suppressing the MDA-MB 231 and MCF-7 cell growth. The findings suggested that these compounds would be very useful for further investigation of the mechanism of cell proliferation, morphology, differentiation and apoptosis in our next research project and some of these may be lead compounds for cancer research.

4. Experimental section

4.1. Chemistry

All commercial reagents and solvents were used as received without further purification unless specified reaction solvents were used for distillation. The reactions were monitored and R_f value were determined using analytical thin layer chromatography (TLC) with Merck Silica gel 60 and F_{254} precoated plates (0.25 mm thickness). Spot on the TLC plates were visualized using ultraviolet light (254 nm). Flash column chromatography was performed with Merck silica gel 60 (100-200 mesh). Melting points were determined in capillaries and are uncorrected. ^{1}H NMR spectra were recorded on Bruker DRX-300, Varian 400 and Varian-500 NMR spectrometers. ^{13}C NMR spectra's were recorded on Bruker DRX-300. Proton chemical shifts are reported in ppm(δ) relative to internal tetramethylsilane (TMS, δ 0.00 or with the solvent reference relative to TMS employed as the internal standard ($CDCl_3$, δ 7.26 ppm; DMSO-d_6 δ 2.54) and multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR 400 spectrometer; data is reported in wave numbers (cm^{-1}). Mass spectra were recorded on Agilent Technologies 1100 Series (Agilent Chemistation Software). High-resolution mass spectra (HRMS) were obtained by using ESI-QTOF mass spectrometry.

*4.2 Synthesis of 2-methyl-4-phenyl-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylic acid (**4**)*

2-Aminobenzothiazole (1 mmol), benzaldehyde (2 mmol), and ethyl acetoacetate (2 mmol) in ethylene glycol (5 mL) were mixed in a flask, and TBAHS (30 mol %) was added at room temperature. The resulting mixture was heated at 120 ^{o}C for 1hr, and completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool, and poured into water (50 mL) and stirred for 15 min, the solid separated was filtered through Buckner funnel and washed with water (2 x 10 mL) and dried over reduced pressure to obtain the crude compound. The above crude compound was dissolved in ethanol (10 mL), added 1*N* potassium hydroxide solution (10 mL) and the reaction mixture was refluxed for 2 hrs, and completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool, and neutralized with diluted hydrochloric acid and stirred for 15 min, the solid separated was filtered through Buckner funnel washed with water (2 x 5 mL), dried over reduced pressure. The above crude product was recrystallized from ethanol to obtain the title compound **4** as a light yellow solid (80 % yield). m.p: 168-172 ^{o}C; IR (KBr, *v*): 3469, 3094, 2822, 1675, 1542, 1456, 1313, 1254, 753, 703 cm^{-1}: ^{1}H NMR (500 MHz, $CDCl_3$+DMSO-d_6): δ 2.48 (s, 3H, CH_3), 6.54 (s, 1H, CH), 7.21-7.39 (m,4H, Ar-H), 7.41- 7.44 (d, 2H, Ar-H), 7.65 (m, 3H, Ar-H). ^{13}C NMR(75 MHz, $CDCl_3$+ DMSO-d_6): 17.1, 57.1, 103.9, 112.7, 122.4, 123.1, 125.1, 125.9, 126.8, 127.6, 127.8, 134.5, 137.3, 159.8, 164.5; MS (ESI): *m/z* 323 $(M+H)^{+}$; HRMS: cacld for $C_{18}H_{15}O_2N_2S$: 323.08487, Found 323.08423.

*4.3 General procedure for the synthesis of compounds (**5a-e**)*

Compound **4** (1mmol) was dissolved in freshly distilled dichloromethane under nitrogen atmosphere .Then HOBt (1.1 mmol), EDC,HCl (1.1 mmol) were added to it. The reaction mixture was stirred for 5 minutes, and piperidine (1.2 mmol) was added slowly followed by the addition of triethylamine (2 mmol) and stirred for 2 hrs at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, water (10 mL) was added to the reaction mixture and extracted with dichloromethane. Organic layer was collected and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the resultant compound was recrystallized with ether to afford **5a** as light brown solid with 79 % yield.

*4.3.1.(2-Methyl-4-phenyl-4H-benzo[4,5]thiazolo[3,2-a]pyrimidin-3-yl)(piperidine-1-yl) methanone (**5a**):* Brown Solid(79% yield): m.p: 154-158 ^{o}C; IR (KBr, *v*): 3537, 3374, 3285,

2934, 2850, 1665, 1634, 1584, 1543, 1467, 1274, 1262, 1207, 1023, 756, 747 cm^{-1}: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08-1.57 (m, 6H, piperidine), 1.84 (s, 3H, CH_3), 2.91-3.02 (m, 4H, piperidine), 6.35 (s, 1H, CH), 6.62 (d, *J* =7.41 Hz,1H, Ar-H), 7.01-7.07 (m, 2H, Ar-H), 7.21-7.24 (m, 2H, Ar-H), 7.29 (m, 3H, Ar-H), 7.37 (d, *J* =7.41 Hz,1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 24.1, 25.2, 42.4, 47.2, 60.1, 107.4, 111.4, 121.6, 123.1, 126.1, 128.3, 129.1, 136.5, 138.3, 140.1, 160.4, 168.1(CO): MS (ESI): *m/z* 390 $(M+H)^+$; HRMS: cacld for $C_{23}H_{24}ON_3S$: 390.16346, Found 390.16272.

*4.3.2.(2-Methyl-4-phenyl-4H-benzo[4,5]thiazolo[3,2-a]pyrimidin-3-yl)(4-methylpiperazin-1-yl)methanone (**5b**):* White solid (75 % yield): m.p: 176-178 ^{o}C; IR (KBr, *v*): 3430, 2928, 2846, 2785, 1600, 1541, 1458, 1430, 1384, 1259, 1206, 1115, 746 cm^{-1}: ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ 1.81 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.41 (m 2H, piperazine), 2.88-3.09 (m, 4H, piperazine), 3.95 (m, 2H, piperazine), 6.30 (s, 1H, CH), 6.74 (d, *J* =7.08 Hz, 1H, Ar-H), 7.10 (m, 2H,Ar-H), 7.26-7.35 (m, 5H, Ar-H), 7.51 (d, *J* =6.90 Hz, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 20.0, 45.1, 53.4, 59.1, 77.7, 78.1, 78.3, 78.5, 106.7, 110.9, 121.5, 121.9, 122.8, 125.6, 125.8, 128.0, 128.7, 137.6, 139.5, 159.2, 167.0; MS (ESI): *m/z* 405 $(M+H)^+$; HRMS: cacld for $C_{23}H_{25}ON_4S$: 405.17436, Found 405.17416.

*4.3.3.(2-Methyl-4-phenyl-4H-benzo[4,5]thiazolo[3,2-a]pyrimidin-3-yl)(morpholino) methanone (**5c**):* Light brown solid (83 % yield): m.p: 218-222 ^{o}C; IR (KBr, *v*): 3435, 3045, 2970, 2910, 2853, 1636, 1611, 1550, 1454, 1423, 1319, 1276, 1204, 1109, 1001, 748, 740 cm^{-1}: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84 (s, 3H, CH_3), 2.89-2.94 (m, 1H, morpholine), 3.0-3.22 (m, 4H,morpholine), 3.59-3.64 (m, 1H, morpholine), 4.0-4.1(m, 2H, morpholine), 6.34(s, 1H, CH), 6.63 (d, *J* = 9.06 Hz, 1H, Ar-H), 7.03-7.07 (m, 2H, Ar-H), 7.29-7.40 (m, 4H, Ar-H), 7.51 (m, 1H, Ar-H), 7.69 (m, 1H, Ar-H). MS (ESI): *m/z* 392 $(M+H)^+$; HRMS: cacld for $C_{22}H_{22}O_2N_3S$: 392.14272, Found 351.14246

*4.3.4.(2-Methyl-4-phenyl-4H-benzo[4,5]thiazolo[3,2-a]pyrimidin-3-yl)(4-phenylpiperazin-1-yl)methanone (**5d**):* White solid (82 % yield): m.p: 194-198 ^{o}C; IR (KBr, *v*): 3435, 3066, 2917, 1635, 1597, 1561, 1466, 1431, 1334, 1234, 1203, 1003, 740 cm^{-1}: ^{1}H NMR (300 MHz, $CDCl_3$): δ δ 1.88 (s, 3H, CH_3), 2.59-2.68 (m, 1H, piperazine), 2.74-2.80 (m, 1H, piperazine), 3.10-3.31 (m, 5H, piperazine), 4.18 (m, 1H, piperazine), 6.37 (s, 1H, CH), 6.61-6.70 (m, 3H, Ar-H), 6.82 (t, *J* =7.55 Hz, 1H, Ar-H), 7.02-7.07 (m, 2H, Ar-H), 7.15-7.24 (m, 3H, Ar-H), 7.29-7.31 (m, 4H, *J* = Ar-H), 7.36-7.40 (m, 1H, Ar-H). ^{13}C NMR (75

MHz, $CDCl_3$): δ 20.6, 29.6, 48.7, 49.5, 60.0, 106.8, 111.4, 116.6, 120.4, 121.7, 122.8, 123.3, 126.0, 126.2, 128.6, 129.0, 129.2, 138.2, 140.1, 150.7, 160.8, 168.3; MS (ESI): *m/z* 467 $(M+H)^+$; HRMS: cacld for $C_{28}H_{27}ON_4S$: 467.19001, Found 467.18756.

*4.3.5.(2-Methyl-4-phenyl-4H-benzo[4,5]thiazolo[3,2-a]pyrimidin-3-yl)(4-(4-nitrophenyl) piperazin-1-yl)methanone (**5e**):* Yellow solid (76.1 % yield): m.p: 222-226 ^oC; IR (KBr, *v*): 3434, 2918, 1634, 1597, 1542, 1398, 1320, 1305, 1278, 1114, 997, 822, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.90 (s, 3H, CH_3), 2.92 (m, 1H, piperazine), 3.09 (m, 1H, piperazine), 3.22-3.27 (m, 3H, piperazine), 3.46 (m, 1H, piperazine), 3.55 (m, 1H, piperazine), 4.25 (m, 1H, piperazine), 6.40 (s, 1H, CH), 6.66 (d, *J* = 8.99Hz, 3H, Ar-H), 7.07-7.12 (m, 2H, Ar-H), 7.21-7.26 (m, 1H, Ar-H), 7.29-7.34 (m, 4H, Ar-H), 7.41-7.43 (m, 1H, Ar-H), 8.09(d, *J* =8.99,2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 45.4, 46.5, 46.7, 60.0, 106.4, 111.5, 112.9, 121.8, 122.8, 123.5, 125.8, 126.0, 126.3, 128.7, 129.3, 138.0, 138.9, 140.3, 154.1, 161.1, 168.6; MS (ESI): *m/z* 512 $(M+H)^+$; HRMS: cacld for $C_{28}H_{26}O_3N_5S$: 512.17509, Found 512.17334.

*4.4 Synthesis of ethyl 3-(2-methyl-4-phenyl-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamido)propanoate (**6**)*

Compound **4** (1mmol) was dissolved in freshly distilled dichloromethane (5 mL) under nitrogen atmosphere. Then HOBt (1.1 mmol), EDC, HCl (1.1mmol) were added to it. The reaction mixture was stirred for 5 minutes, and *β*-alanine ethyl ester hydrochloride (1.5 mmol) was added slowly, followed by the addition of triethylamine (2 mmol) and stirred for 2 h at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, water (10 mL) was added to the reaction mixture and extracted with dichloromethane. Organic layer was collected and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the resultant compound was recrystallized with ether to afford the title compound **6** as pale brown solid with 62% yield. m.p: 148-151 ^oC; IR (KBr, *v*): 3235, 3044, 2989, 2939, 1728, 1642, 1623, 1583, 1536, 1473, 1334, 1324, 1296, 1208, 1190, 1154, 1027, 753, 693 cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, *J* =7.55, 6.79 Hz,3H, CH_3), 2.12 (s, 3H, CH_3), 2.39-2.52 (m, 2H, $COCH_2$), 3.42-3.52 (m, 2H, CH_2), 4.00-4.13 (m, 2H, $NHCH_2$), 5.96 (bt, 1H, NH), 6.40 (s, 1H, CH), 6.83-6.86 (d, *J* =7.55 Hz, 1H, Ar-H), 7.04-7.32 (m, 6H, Ar-H), 7.38-7.40 (d, *J* = 7.55 Hz, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 21.7, 33.7, 34.7, 58.4, 60.5, 109.5, 111.4, 121.7, 123.0,

123.3, 126.2, 128.1, 128.8, 138.1, 140.5, 141.3, 168.0, 172.3; MS (ESI): *m/z* 422 $(M+H)^+$; HRMS: cacld for $C_{23}H_{24}O_3N_3S$: 422.15329, Found 422.15244.

*4.5 Synthesis of 3-(2-methyl-4-phenyl-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamido)propanoic acid (**7**)*

The compound **6** (1.2 mmol) was dissolved in ethanol (10 mL), added 1*N* potassium hydroxide solution (10 mL) and the reaction mixture was refluxed for 1 hr, and completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool to room temperature, neutralized with diluted hydrochloric acid and the solid separated was filtered through Buckner funnel and washed with water and dried over reduced pressure to obtain the crude compound. The above crude product was recrystallized from ethanol to obtain the title compound **7** as a light green solid (65 % yield). m.p: 142-146 ^oC; IR (KBr, *v*): 3318, 2924, 2852, 1624, 1526, 1456, 1259, 1206, 1122, 749, 699 cm^{-1}: ^1H NMR (300MHz, DMSO-d_6): δ 2.08 (s, 3H, CH_3), 2.37-2.42 (m, 2H, $COCH_2$), 3.42-3.44 (m, 2H, $NHCH_2$), 6.47 (s, 1H, CH), 6.92-6.95 (d, *J* =7.93 Hz, 1H, Ar-H), 7.07-7.31 (m, 7H, Ar-H), 7.50 (d, *J* =7.17Hz, 1H, Ar-H), 7.56 (broad, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.3, 34.7, 35.7, 57.2, 109.5, 111.4, 122.1, 122.5, 123.3, 126.1, 126.4, 128, 128.7, 137.8, 140.6, 141.4,159.5,166.6; MS (ESI): *m/z* 394 $(M+H)^+$; HRMS: cacld for $C_{21}H_{20}O_3N_3S$: 394.12199, Found 394.12210.

*4.6 General procedure for the synthesis of compounds (**8a-e**)*

Compound **7** (1 mmol) was dissolved in freshly distilled dichloromethane (5 mL) under nitrogen atmosphere. Then HOBt (1.1 mmol), EDC, HCl (1.1 mmol) were added to it. The reaction mixture was stirred for 5 minutes, piperidine (1.2 mmol) was added in a slow stream and followed by the addition of triethylamine (2 mmol) and the reaction mixture was stirred for 1 hr at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, water (10 mL) was added to the reaction mixture and extracted with dichloromethane. Organic layer was collected and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the resultant compound was recrystallized with ether to afford **8a** as brick red solid with 81% yield.

*4.6.1.2-Methyl-N-(3-oxo-3-(piperidin-1-yl)propyl)-4-phenyl-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide(**8a**):* Brick red solid (81% yield): m.p: 152-155 ^oC; IR (KBr, *v*): 3276, 2936, 2856, 1632, 1613, 1541, 1471, 1326, 1208, 1026, 829, 743, 699 cm^{-1}: ^1H

NMR (500 MHz, $CDCl_3$): δ 1.41-1.71(m, 6H, piperidine), 2.14 (s, 3H, CH_3), 2.25-2.30 (m, 1H, $COCH_2$), 2.42-2.47 (m, 1H, $COCH_2$), 3.26-3.31(m, 2H, CH_2), 3.38-3.57 (m, 4H, piperidine), 6.34 (bt, 1H, NH), 6.40 (s, 1H, CH), 6.84-6.87 (d,*J* =7.34 Hz, 1H, Ar-H), 7.04-7.07 (t, *J* =7.34 Hz, 1H, Ar-H), 7.10-7.14 (t, *J* =8.39, 7.34 Hz, 1H, Ar-H), 7.17-7.20 (m, 1H, Ar-H), 7.23-7.25 (m, *2H*, Ar-H), 7.32-7.34 (d, *J*=6.29 Hz, 2H, Ar-H), 7.37-7.39 (d, *J* =7.34 Hz,1H,Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8, 24.4, 25.4, 26.2, 32.7, 35.0, 42.6, 46.2, 58.6, 109.6, 111.4, 121.8, 123.3, 126.2, 126.5, 128.1, 128.7, 138.3, 140.7, 161.1, 167.9(CO), 169.4(CO); MS (ESI): *m/z* 461 $(M+H)^+$; HRMS: cacld for $C_{26}H_{29}O_2N_4S$: 461.20057, Found 461.19897.

*4.6.2.2-Methyl-N-(3-(4-methylpiperazin-1-yl)-3-oxopropyl)-4-phenyl-4H-benzo[4,5]thiazolo [3,2-a]pyrimidine-3-carboxamide (**8b**):* White solid (71% yield): m.p: 162-166 ^{o}C; IR (KBr, *v*): 3435, 2932, 1646, 1540, 1444, 1208, 746, 702 cm^{-1}: ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.11(s, 3H,CH_3), 2.29(s, 3H, CH_3), 2.30-2.48(m,4H, $COCH_2$ & piperazine), 3.38-3.63 (m, 8H, $NHCH_2$ & piperazine), 6.42 (s, 1H, CH), 6.89 (d, *J* = 7.36 Hz, 1H, Ar-H), 7.06-7.35 (m, 7H, Ar-H), 7.44 (d, *J* = 7.55 Hz, 1H, Ar-H), 7.60 (bt, 1H, NH). MS (ESI): *m/z* 476 $(M+H)^+$; HRMS: cacld for $C_{26}H_{30}O_2N_5S$: 476.21147, Found 476.21155, cacld for $C_{26}H_{29}O_2N_5NaS$: 498.19342, Found 498.19351:

*4.6.3.2-Methyl-N-(3-morpholino-3-oxopropyl)-4-phenyl-4H-benzo[4,5]thiazolo[3,2-a]pyri midine-3-carboxamide (**8c**):* Pale brown solid (75 % yield): m.p: 198-202 ^{o}C; IR (KBr, *v*): 3435, 3263, 3062, 1646, 1542, 1470, 1332, 1209, 1111, 745 cm^{-1}: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H, CH_3), 2.28 (m, 1H, $COCH_2$), 2.43 (m, 1H, $COCH_2$), 3.31-3.39 (m, 2H, morpholine), 3.44-3.55 (m, 2H, CH2), 3.56-3.67 (m, 6H, morpholine), 6.27 (t,1H, NH), 6.41 (s, 1H, CH), 6.87 (d, *J* =7.55Hz,1H, Ar-H), 7.04-7.17 (m, 2H, Ar-H), 7.20-7.24 (m, 2H, Ar-H), 7.28-7.36 (m, 3H, Ar-H), 7.40 (d,*J* =7.55Hz,1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 32.5, 34.8, 41.7, 45.4, 58.5, 66.3, 66.7, 111.4, 121.8, 123.3, 126.2, 126.5, 128.1, 128.6, 163.3, 168.0; MS (ESI): *m/z* 463 $(M+H)^+$; HRMS: cacld for $C_{25}H_{27}O_3N_4S$: 463.17984, Found 463.17868.

*4.6.4.2-Methyl-N-(3-oxo-3-(4-phenylpiperazin-1-yl)propyl)-4-phenyl-4H-benzo[4,5]thiazolo [3,2-a]pyrimidine-3-carboxamide (**8d**):* White solid (82 % yield): m.p:173-176 ^{o}C; IR (KBr, *v*): 3401, 2922, 1637, 1599, 1502, 1467, 1332, 1231, 1026, 753 cm^{-1}: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 3H,CH_3), 2.29-2.38 (m, 1H, $COCH_2$), 2.47-2.56 (m,1H, CH_2),

3.08-3.18 (m, 4H, piperazine), 3.47-3.60 (m, 4H, piperazine), 3.62-3.66 (m, 1H, CH_2), 3.72-3.78 (m, 1H, CH_2), 6.31(bt, 1H, NH), 6.41(s, 1H, CH), 6.85-6.94 (m, 4H, Ar-H), 7.04-7.41 (m, 10H, Ar-H). MS (ESI): *m/z* 538 $(M+H)^+$; HRMS: cacld for $C_{31}H_{32}O_2N_5S$: 538.22712, Found 538.22583.

*4.6.5.2-Methyl-N-(3-(4-(4-nitrophenyl)piperazin-1-yl)-3-oxopropyl)-4-phenyl-4H-benzo [4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (**8e**):* Yellow solid (89 % yield): m.p: 166-168 ^oC; IR (KBr, *v*): 3435, 2919, 1657, 1631, 1596, 1542, 1327, 1238, 1208, 1116, 1026, 830, 753, 699 cm^{-1}: ^1H NMR (500 MHz, $CDCl_3$+DMSO-d_6): δ 2.13 (s, 3H, CH_3), 2.41-2.56 (m, 2H, $COCH_2$), 3.45-3.52 (m, 6H, piperazine), 3.62 (m, 2H,CH_2), 3.73 (m, 2H, piperazine), 6.44 (s, 1H, CH), 6.87-6.93 (m, 3H, Ar-H), 7.05 (bt, 1H, NH), 7.09 (t, 1H, Ar-H), 7.15-7.19 (q, 2H, Ar-H), 7.24-7.27 (t, 2H, Ar-H), 7.31-7.33 (d, *J* =7.41 Hz, 2H, Ar-H), 7.44 (d, *J* =8.47 Hz,1H, ArH), 7.63 (s, 2H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$+ DMSO-d_6): δ 21.3, 32.1, 34.6, 43.8, 46.0, 57.8, 108.8, 110.8, 112.2, 121.4, 122.4, 122.9, 125.3, 125.9, 127.6, 128.1, 137.6, 138.1, 140.1, 141.2, 153.7, 160.4, 167.4(CO), 169.4(CO); MS (ESI): *m/z* 583 $(M+H)^+$; HRMS: cacld for $C_{31}H_{31}O_4N_6S$: 583.21220, Found 583.21167.

In vitro cytotoxicity testing

Cytotoxicity of the synthesized compounds was assessed on the basis of the measurement of the *in vitro* growth in the 96 well plates by cell-mediated reduction of tetrazolium salt to water insoluble formazan crystals by a previously described method [17]. Cell lines for testing *in vitro* cytotoxicity included HeLa derived from human cervical cancer cells (ATCC No. CCL-2), A549 derived from human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185), MDA-MB-231 derived from human breast adenocarcinoma cells (ATCC No. HTB-26) and MCF7 derived from human breast adenocarcinoma cells (ATCC No. HTB-22) were obtained from American Type Culture Collection, Manassas, VA, USA. Doxorubicin was used as positive control for comparison purpose. Dose-response curves were plotted for the test compounds and controls after correction by subtracting the background absorbance from that of the blanks. The antitumor potency of the compounds indicated by IC_{50} values (50% inhibitory concentration) were calculated from the plotted absorbance data for the dose-response curves. IC_{50} values (in μM) are expressed as the average of two independent experiments.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds.

Figure/Scheme Captions:

Scheme 1: Synthesis of 2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylic acid.

Scheme 2: Synthesis of (2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-3-yl)(piperidine/4-methylpiperazin/morpholino/4-phenylpiperazin/4-nitrophenyl) piperazin -1-yl) methanone derivatives.

Scheme 3: Synthesis of 2-methyl-*N*-(3-oxo-3-(piperidine/4-methylpiperazin/morpholino/4-phenylpiperazin/4-nitrophenyl)-1-yl)propyl)-4-phenyl-4*H*-benzo[4,5]thiazolo [3,2-*a*]pyrimidine-3-carboxamides.

Table 1: IC_{50} of the tested compounds against human tumor cell lines

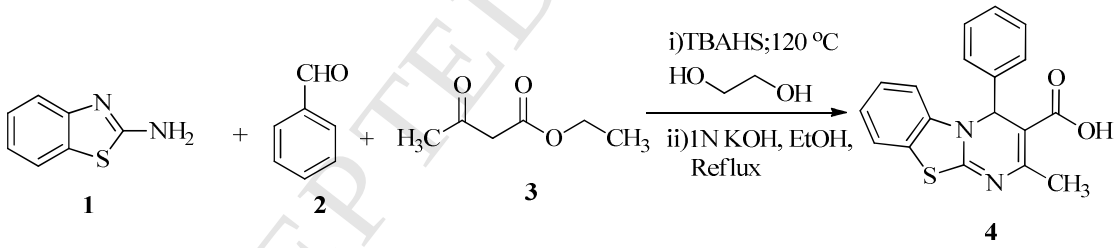
Table

Table 1: Cytotoxicity of the tested compounds against human tumor cell lines

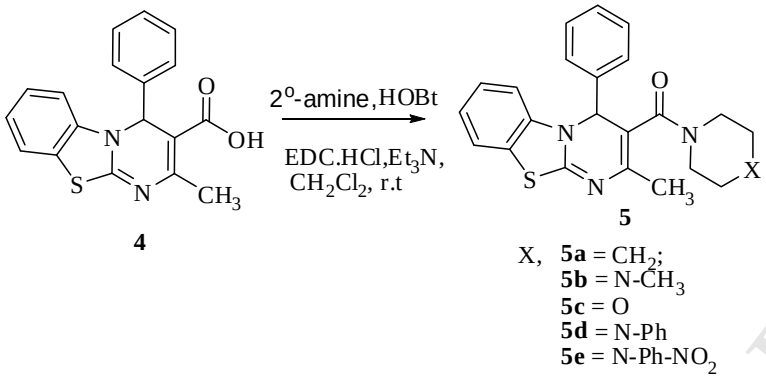
Compounds	IC_{50}[a] (µM)			
	HeLa	**MDA-MB-231**	**MCF-7**	**A549**
5a	-	5.01	11.74	-
5b	-	1.58	0.58	-
5c	-	11.09	10.084	-
5d	-	31.58	77.58	-
5e	-	47.25	29.01	-
8a	11.39	21.73	16.79	18.09
8b	-	-	-	-
8c	-	-	-	-
8d	-	-	-	-
8e	25.69	-	13.79	11.18
Dox[b]	0.451	0.501	1.05	1.21

[a] Data presented is the mean value of two independent determinations.
[b] Doxorubicin is positive control

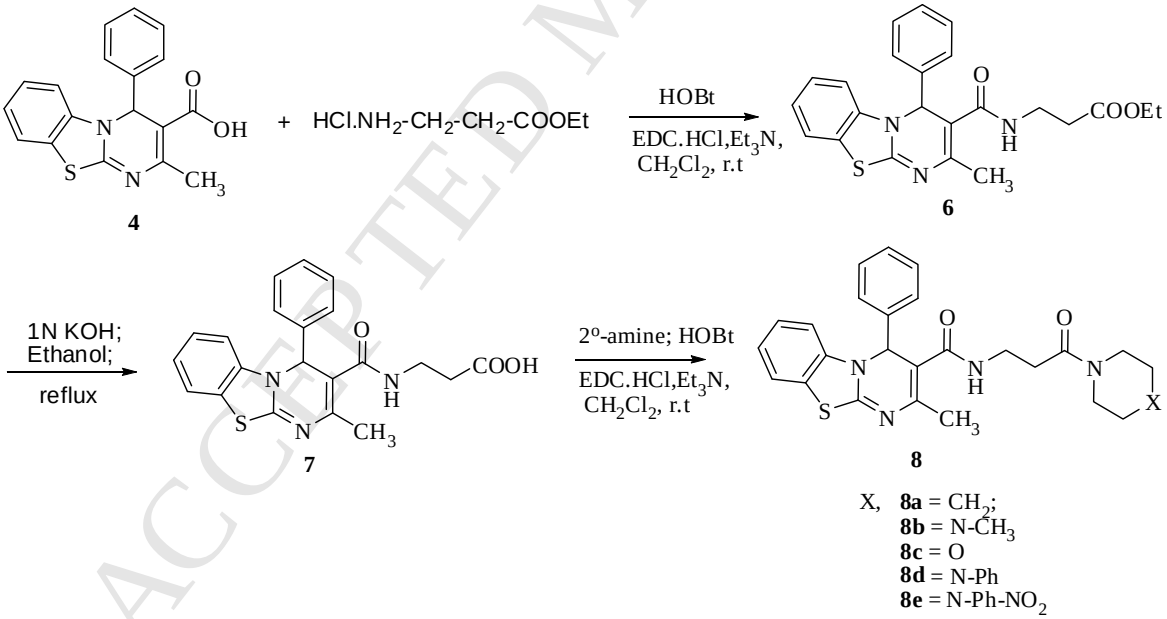
Schemes



Scheme 1: Synthesis of 2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine-3-carboxylic acid.



Scheme 2: Synthesis of (2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-3-yl)(piperidine/4-methylpiperazin/morpholino/4-phenylpiperazin/4-nitrophenyl) piperazin -1-yl) methanone derivatives.



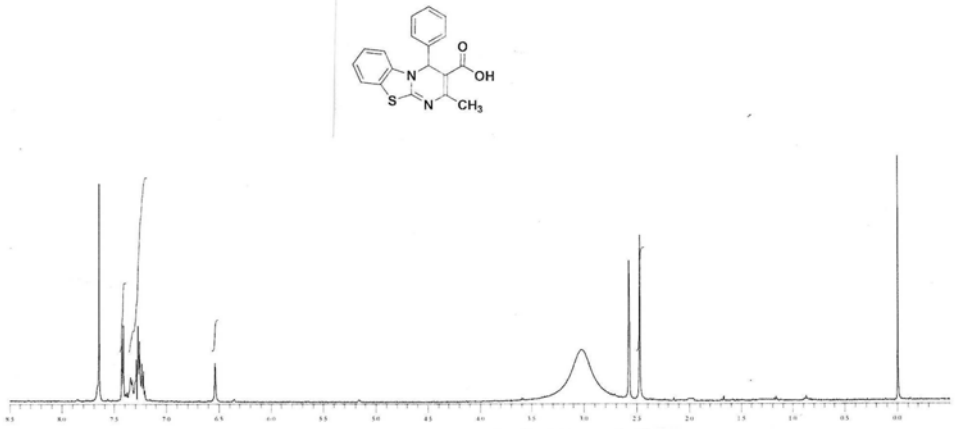
Scheme 3: Synthesis of 2-methyl-*N*-(3-oxo-3-(piperidine/4-methylpiperazin/morpholino/4-phenylpiperazin/4-nitrophenyl)-1-yl)propyl)-4-phenyl-4*H*-benzo[4,5] thiazolo[3,2-a]pyrimidine-3-carboxamides.

Research Highlights

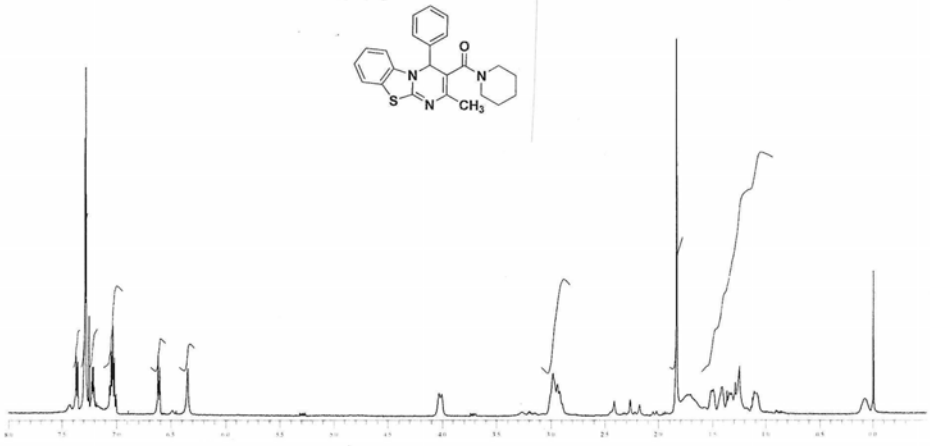
- **To discover and develop tumor growth inhibitors.**
- **Synthesis of several new benzo[4,5]thiazolo[1,2-*a*]pyrimidine-3-carboxylate analogues**
- **Compound 5a and 5b exhibited potent cytotoxicity against MDA-MB-231 and MCF-7 cells.**

Synthesis of Novel Benzo[4,5]thiazolo[1,2-*a*]pyrimidine-3-carboxylate Derivatives and Biological Evaluation as Potential Anticancer Agents

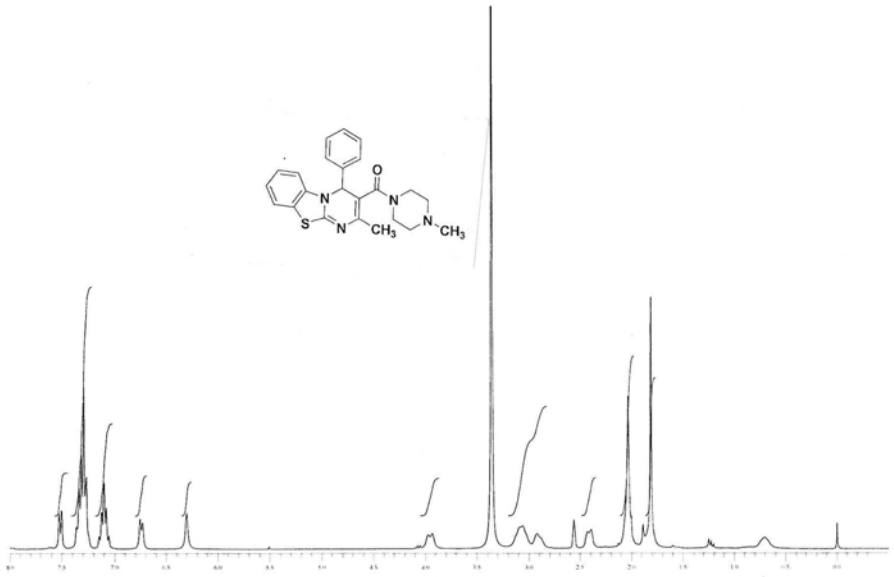
Lingaiah Nagarapu[a],*, Satheeshvarma Vanaparthi[a], Rajashaker Bantu[a], Ganesh Kumar C[b]



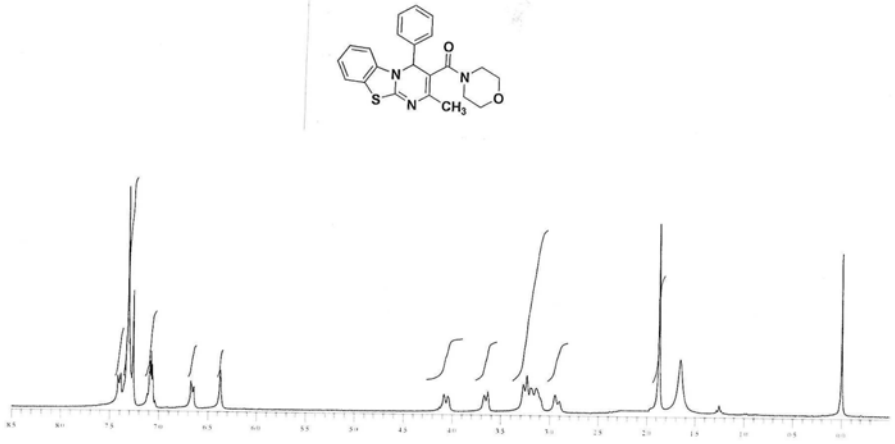
^{1}H NMR Spectrum of compound 2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylic acid (4)



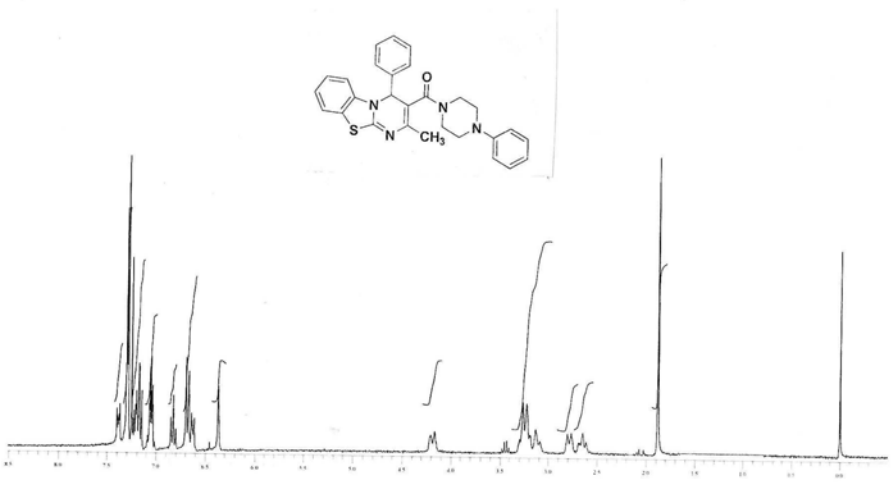
^{1}H NMR Spectrum of (2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-3-yl)(piperidine-1-yl) methanone (5a):



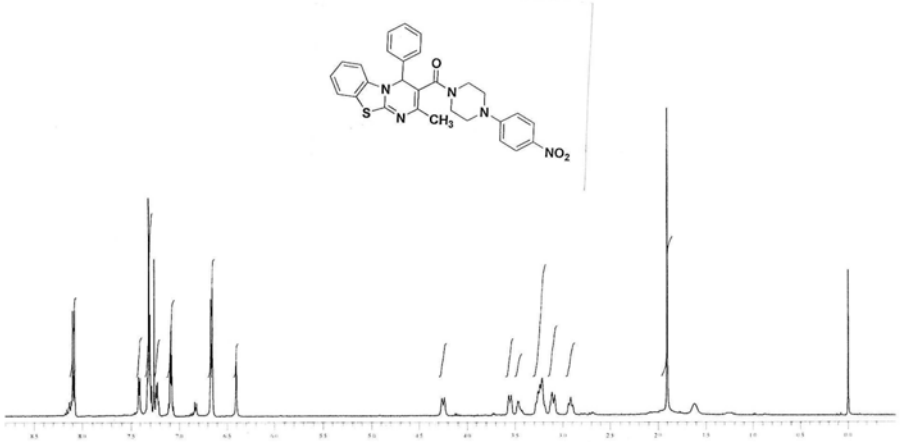
^{1}H NMR Spectrum of (2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-3-yl)(4-methylpiperazin-1-yl)methanone (5b):



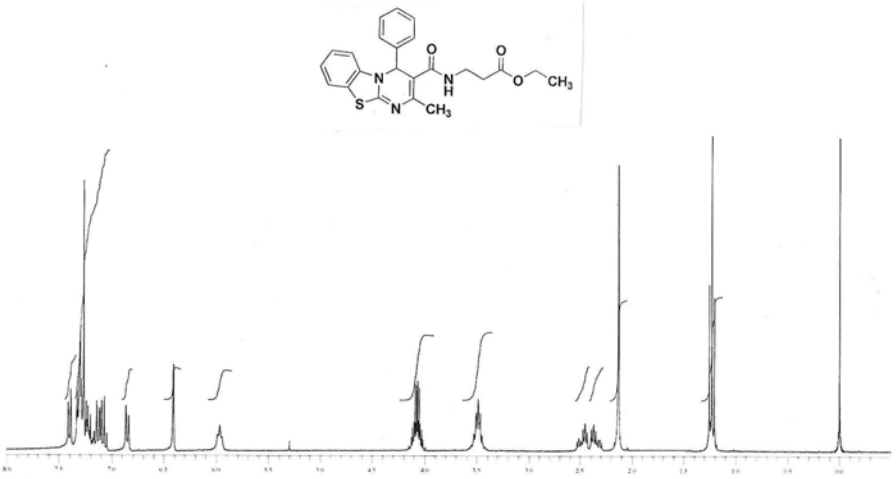
^{1}H NMR Spectrum of compound (2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-3-yl)(morpholino)methanone (5c)



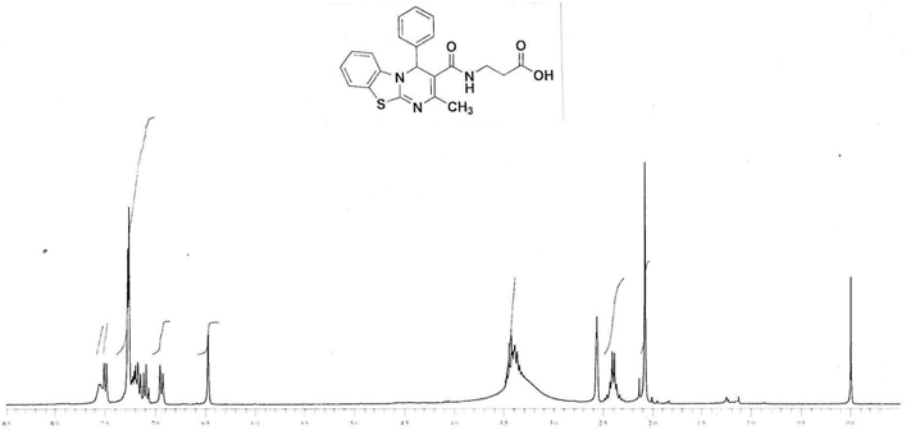
^{1}H NMR Spectrum of compound (2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-3-yl)(4-phenylpiperazin-1-yl)methanone (5d)



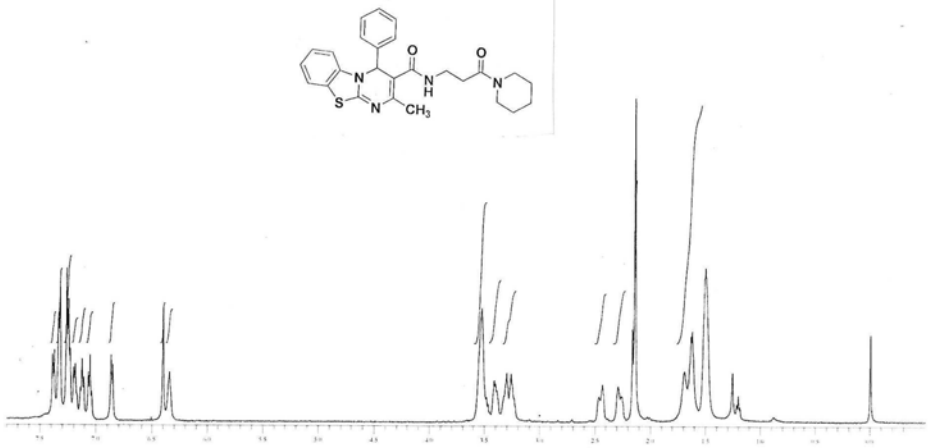
^{1}H NMR Spectrum of compound (2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-3-yl)(4-(4-nitrophenyl)piperazin-1-yl)methanone (5e)



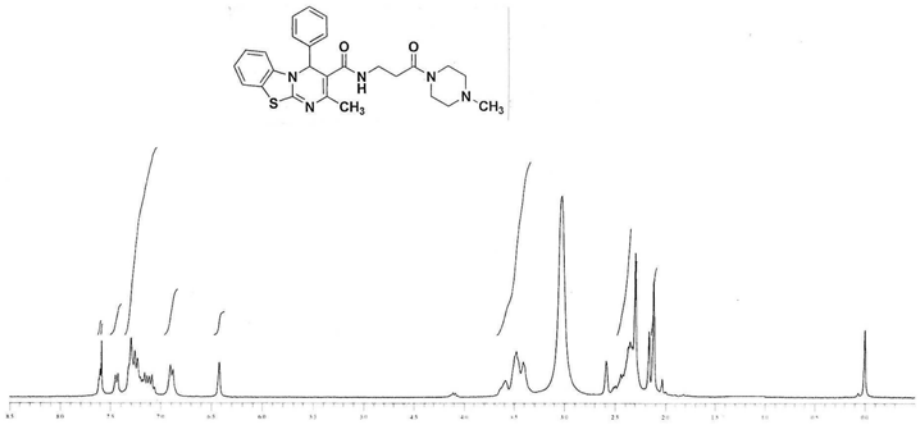
^{1}H NMR Spectrum of compound Ethyl 3-(2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamido) propanoate (6)



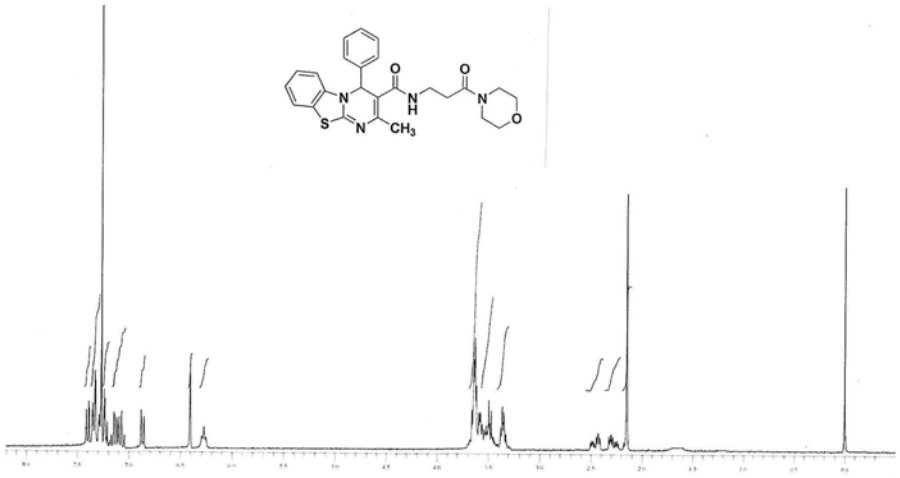
^{1}H NMR Spectrum of compound 3-(2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamido) propanoic acid (7)



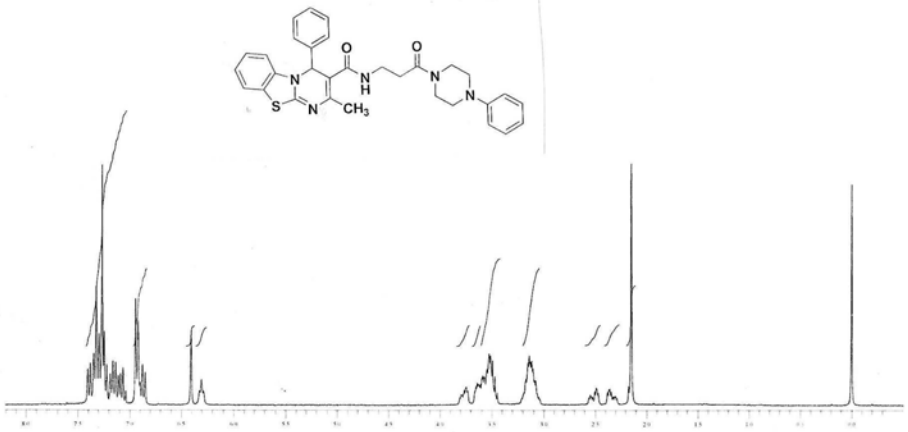
^{1}H NMR Spectrum of compound2-Methyl-N-(3-oxo-3-(piperidin-1-yl)propyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (8a)



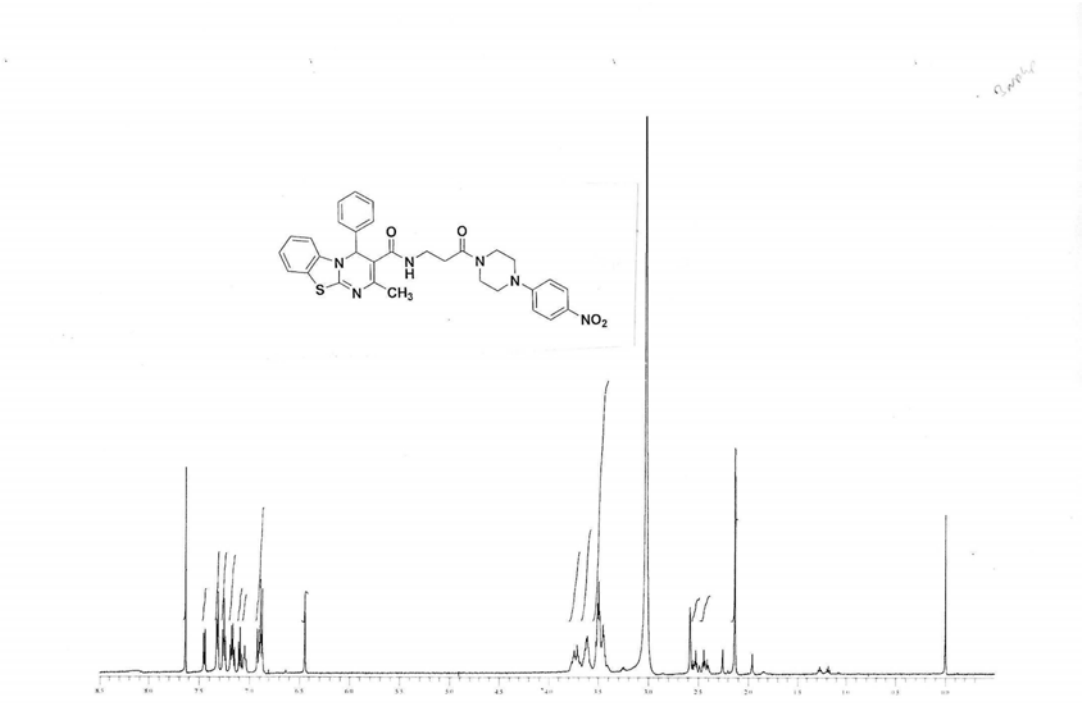
^{1}H NMR Spectrum of compound 2-Methyl-N-(3-(4-methylpiperazin-1-yl)-3-oxopropyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (8b)



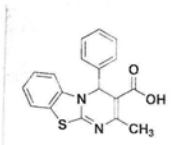
^{1}H NMR Spectrum of compound 2-Methyl-N-(3-morpholino-3-oxopropyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (8c)

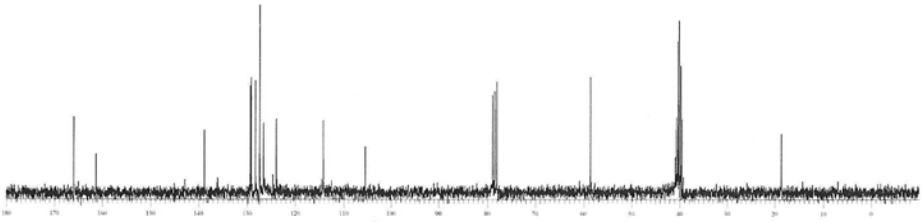


^{1}H NMR Spectrum of compound 2-Methyl-N-(3-oxo-3-(4-phenylpiperazin-1-yl)propyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (8d)

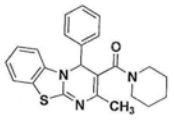


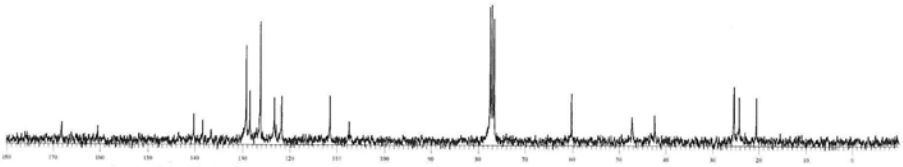
^{1}H NMR Spectrum of compound 2-Methyl-N-(3-(4-(4-nitrophenyl)piperazin-1-yl)-3-oxopropyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (8e)



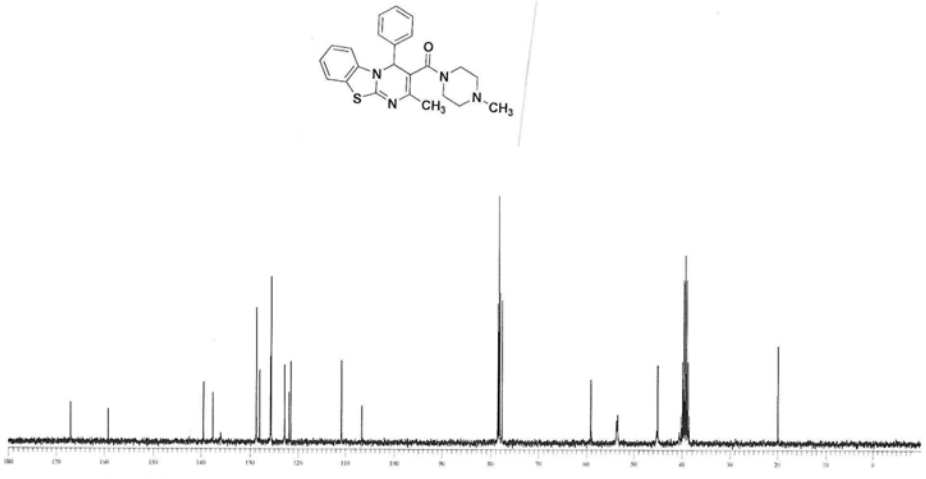


^{13}C NMR Spectrum of compound 2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylic acid (4)

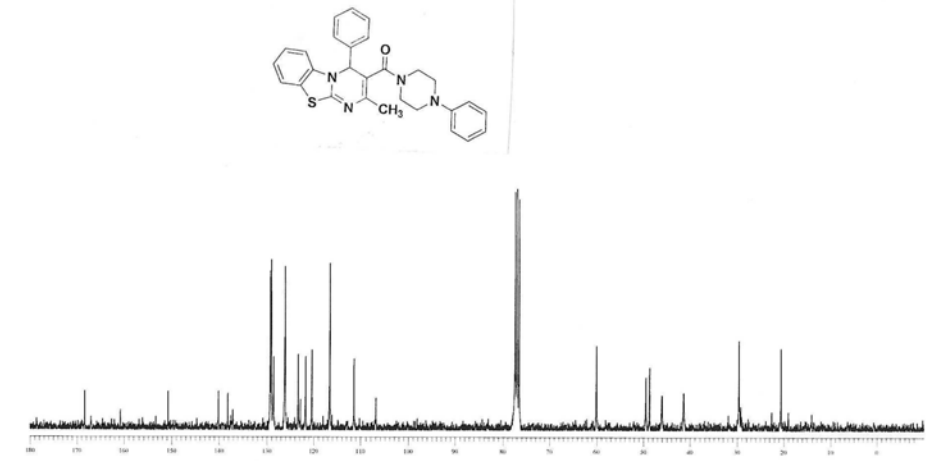




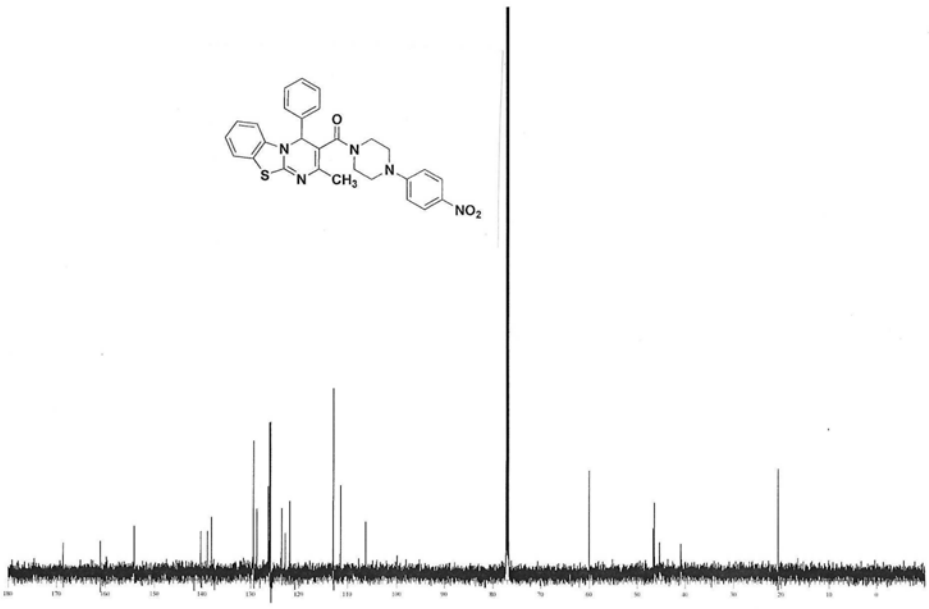
^{13}C NMR Spectrum of (2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-3-yl)(piperidine-1-yl) methanone (5a):



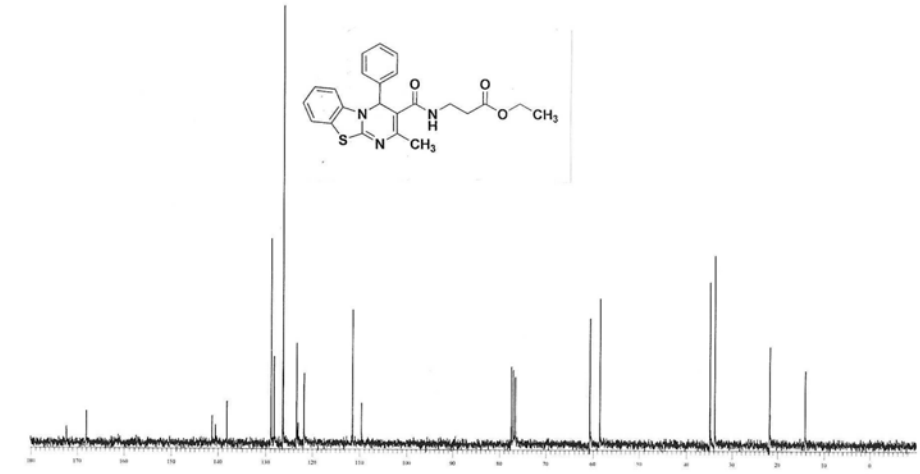
^{13}C NMR Spectrum of (2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-3-yl)(4-methylpiperazin-1-yl)methanone (5b):



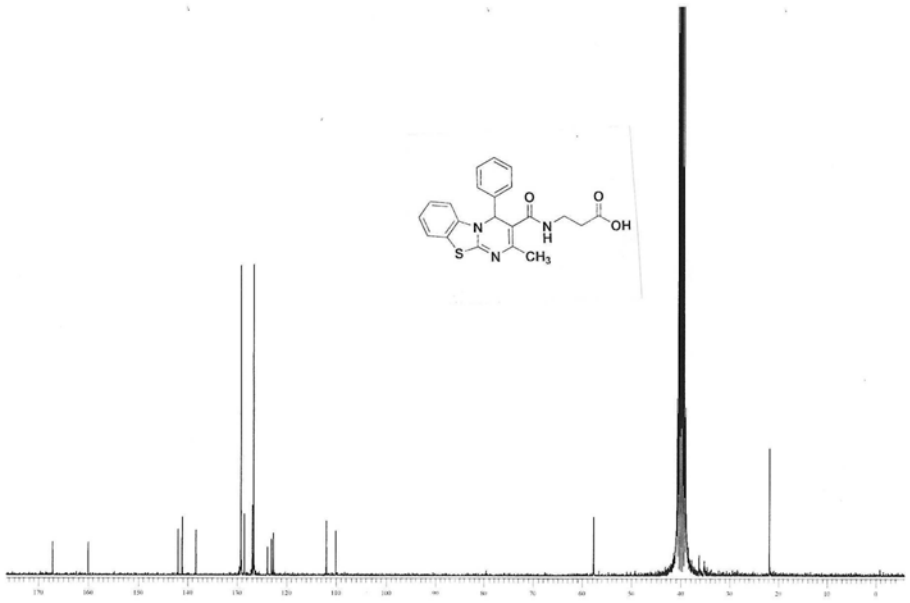
^{13}C NMR Spectrum of compound (2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-3-yl)(4-phenylpiperazin-1-yl)methanone (5d)



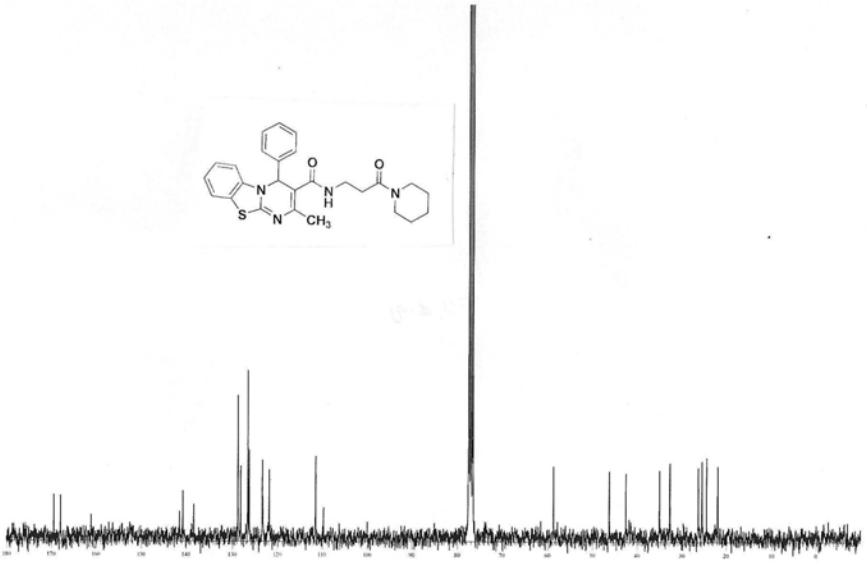
^{13}C NMR Spectrum of compound (2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-3-yl)(4-(4-nitrophenyl)piperazin-1-yl)methanone (5e)



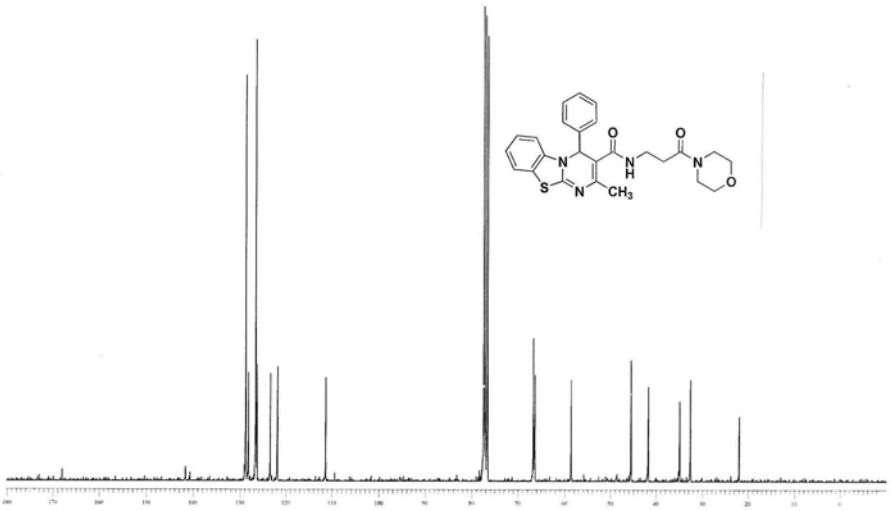
^{13}C NMR Spectrum of compound Ethyl 3-(2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamido) propanoate (6)



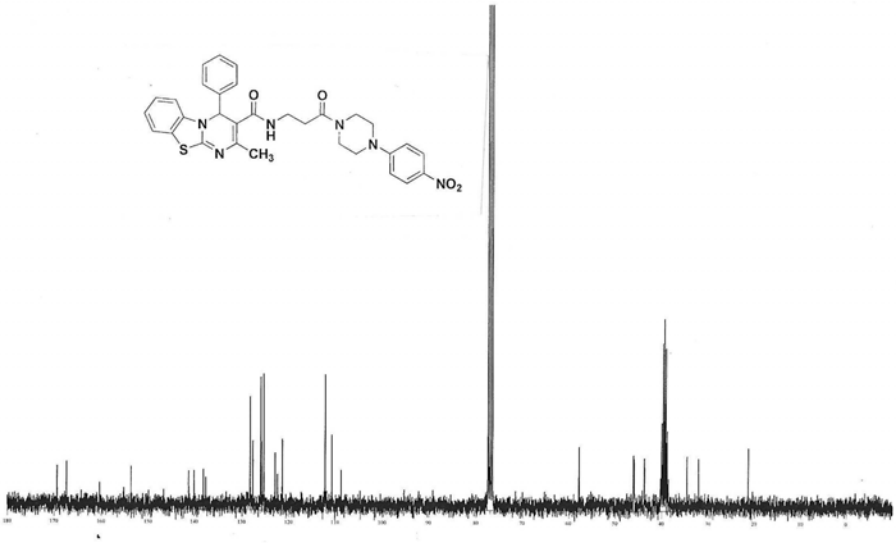
^{13}C NMR Spectrum of compound 3-(2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamido) propanoic acid (7)



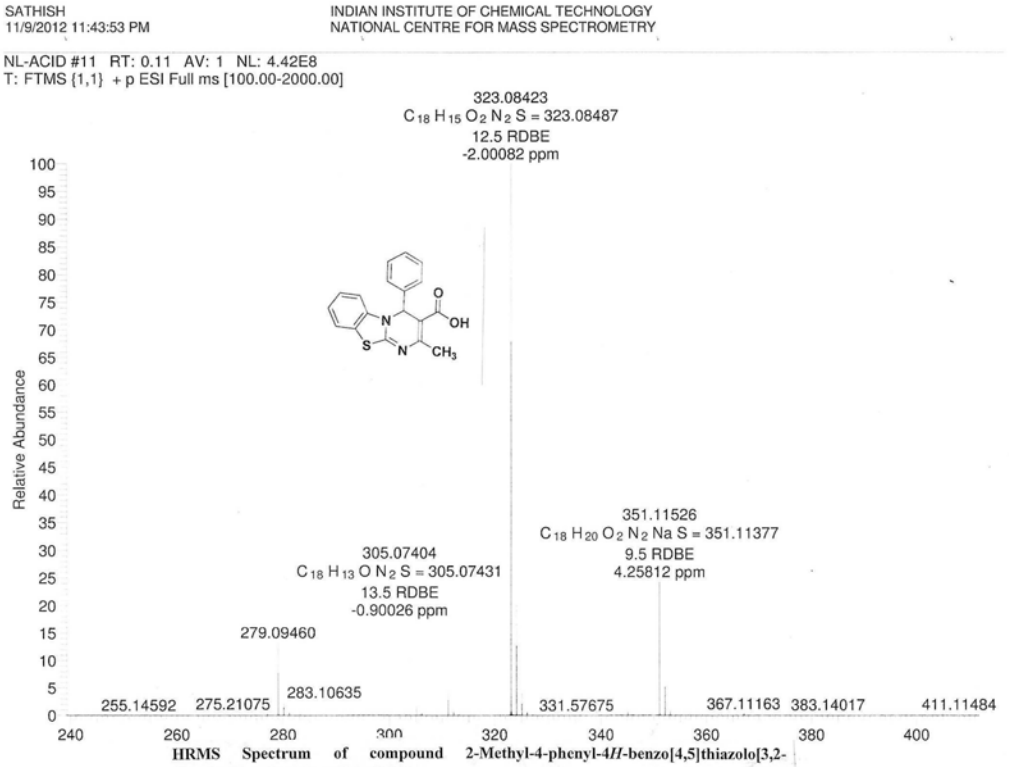
^{13}C NMR Spectrum of compound 2-Methyl-N-(3-oxo-3-(piperidin-1-yl)propyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (8a)



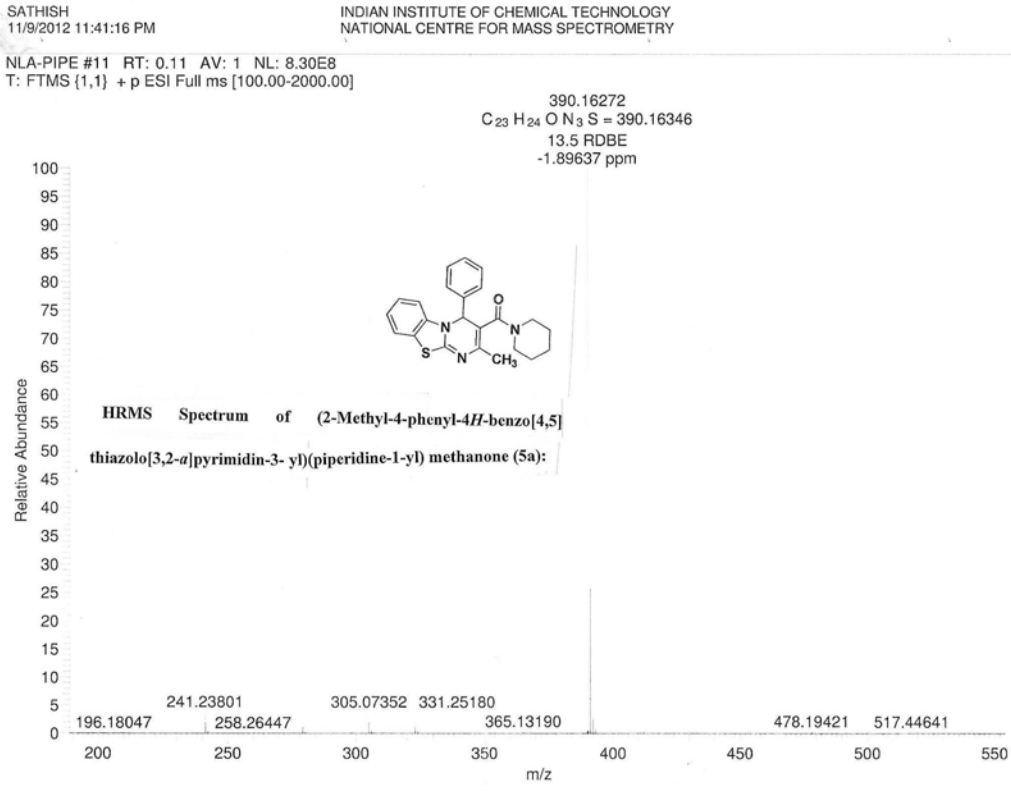
^{13}C NMR Spectrum of compound 2-Methyl-N-(3-morpholino-3-oxopropyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (8c)



^{13}C NMR Spectrum of compound 2-Methyl-N-(3-(4-(4-nitrophenyl)piperazin-1-yl)-3-oxopropyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (8e)



HRMS Spectrum of compound 2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylic acid (4)



HRMS Spectrum of (2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-3- yl)(piperidine-1-yl) methanone (5a):

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INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
NATIONAL CENTRE FOR MASS SPECTROMETRY

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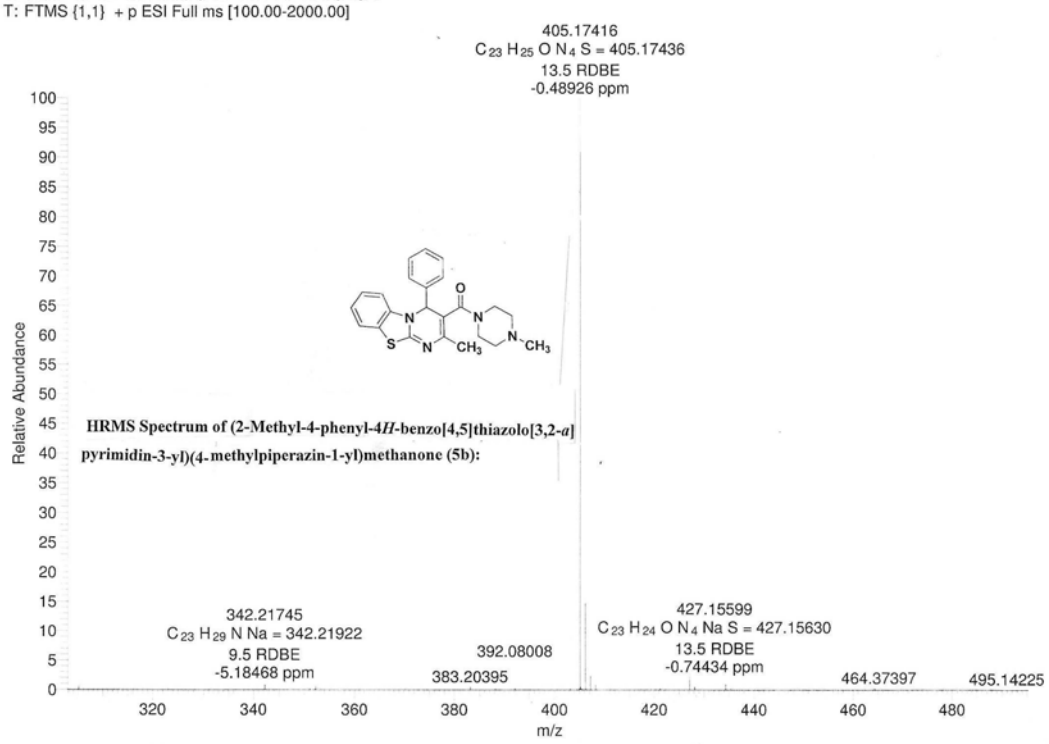

HRMS Spectrum of (2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-*a*] pyrimidin-3-yl)(4-methylpiperazin-1-yl)methanone (5b):

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11/16/2012 9:10:55 PM

INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
NATIONAL CENTRE FOR MASS SPECTROMETRY

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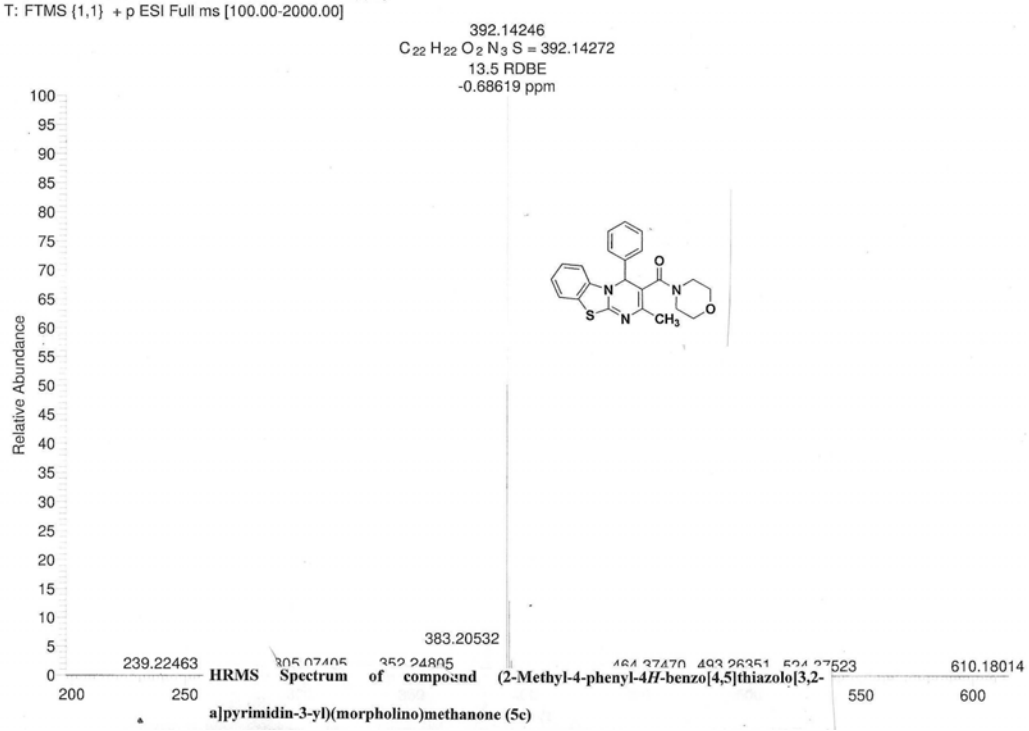
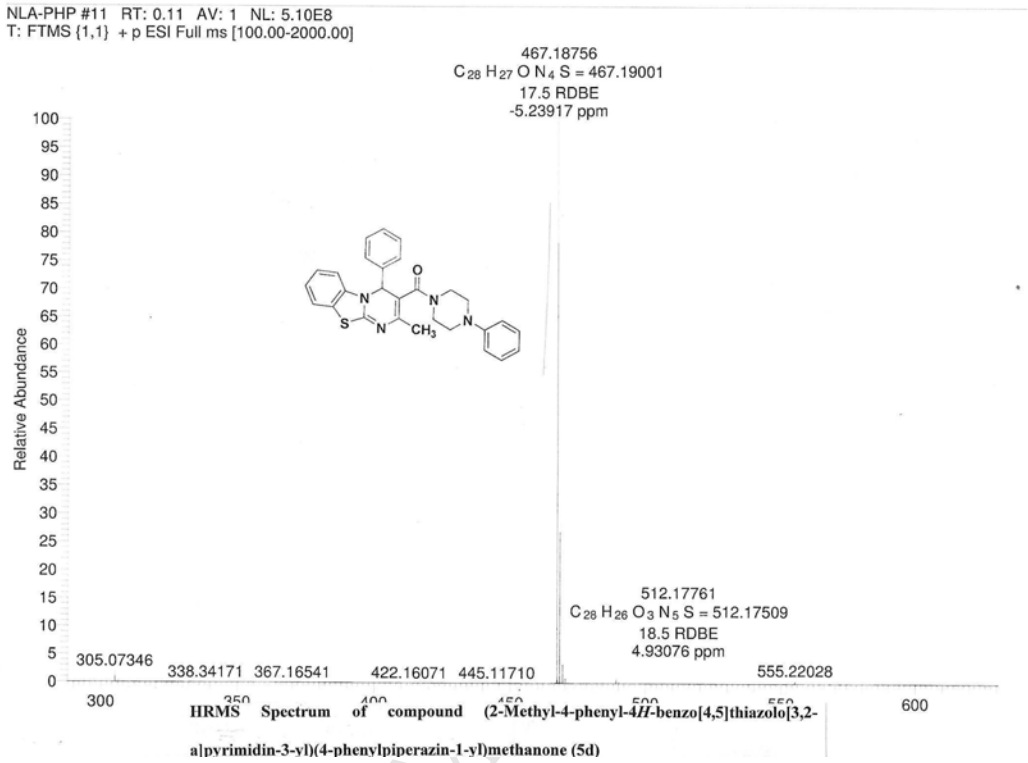


HRMS Spectrum of compound (2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-3-yl)(morpholino)methanone (5c)



HRMS Spectrum of compound (2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-3-yl)(4-phenylpiperazin-1-yl)methanone (5d)

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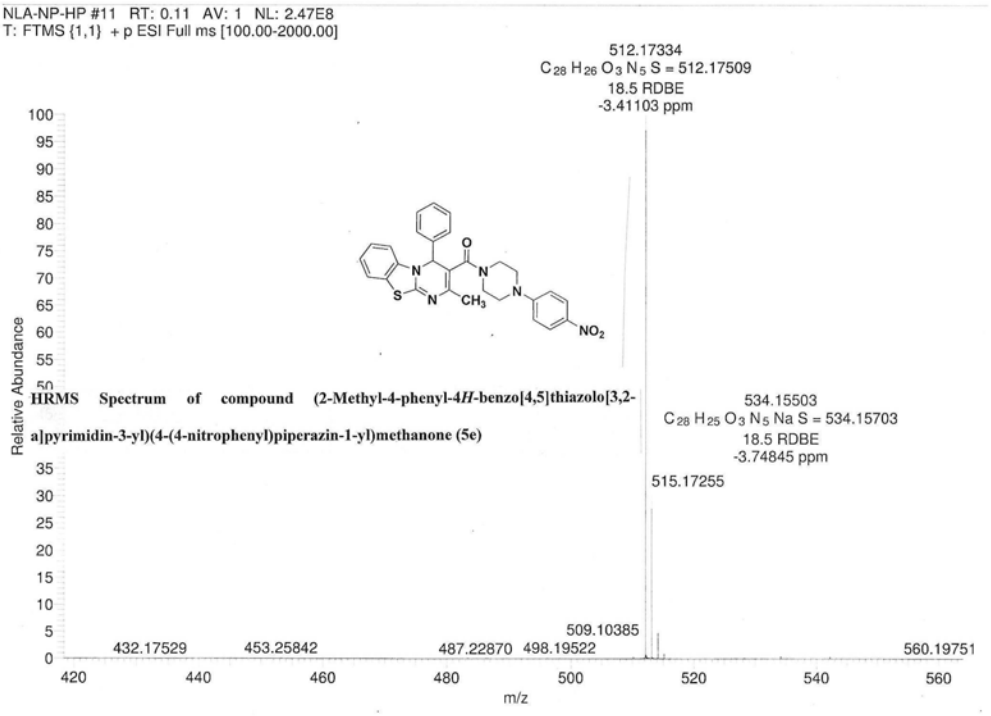
NATIONAL CENTRE FOR MASS SPECTROMETRY



HRMS Spectrum of compound (2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-3-yl)(4-(4-nitrophenyl)piperazin-1-yl)methanone (5e)

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11/16/2012 9:16:08 PM

INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
NATIONAL CENTRE FOR MASS SPECTROMETRY

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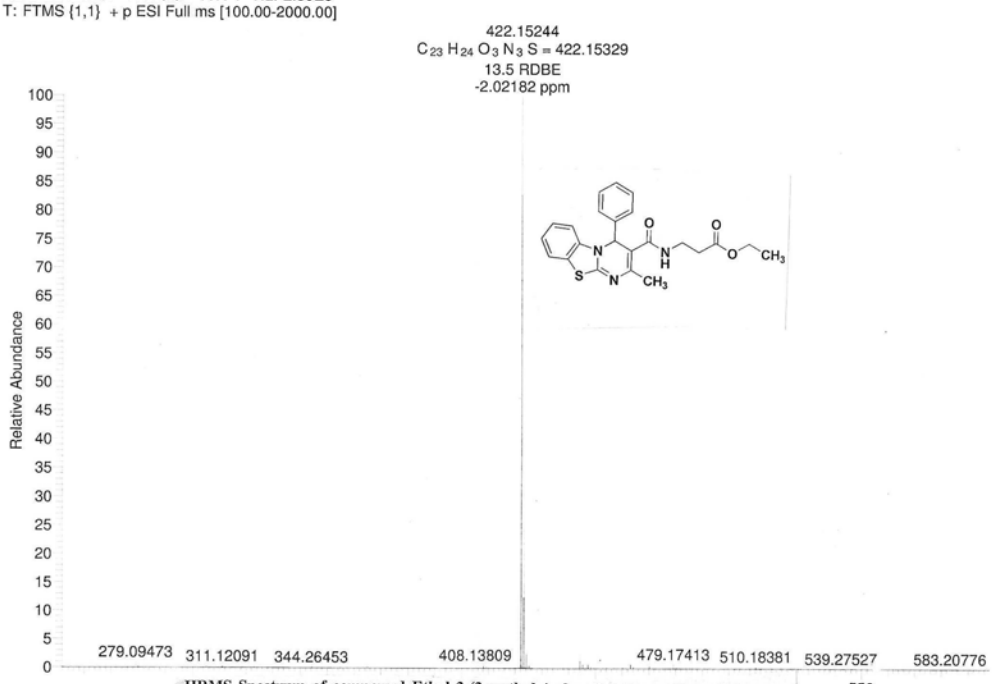

HRMS Spectrum of compound Ethyl 3-(2-methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamido) propanoate (6)

SATHEEESH
11/16/2012 9:18:43 PM

INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
NATIONAL CENTRE FOR MASS SPECTROMETRY

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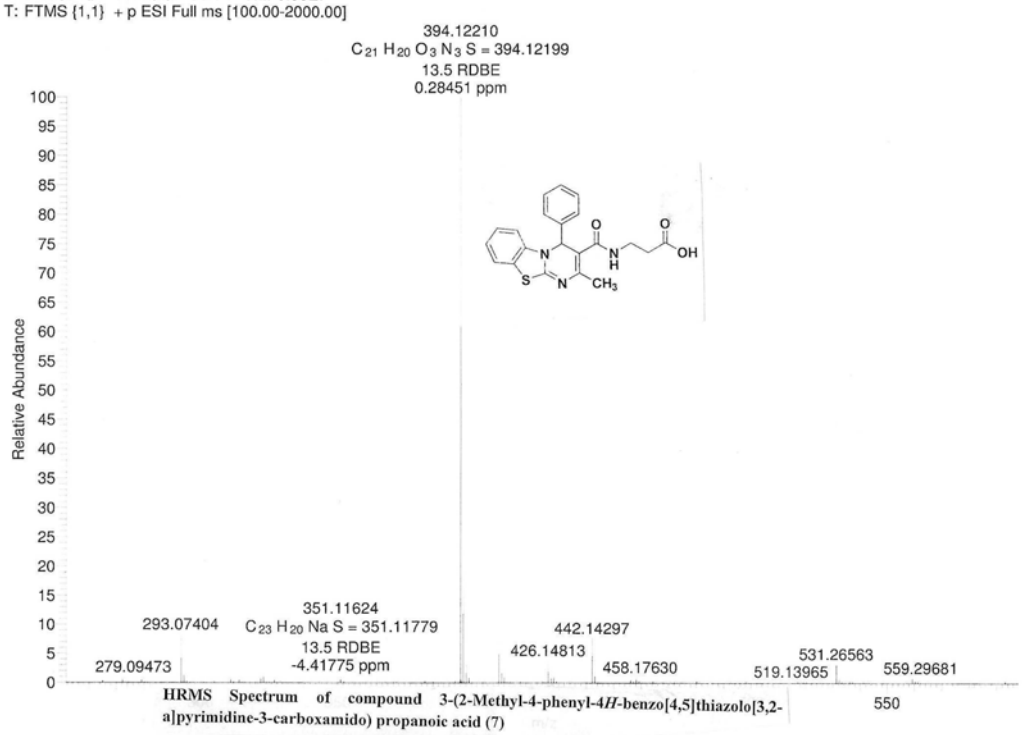
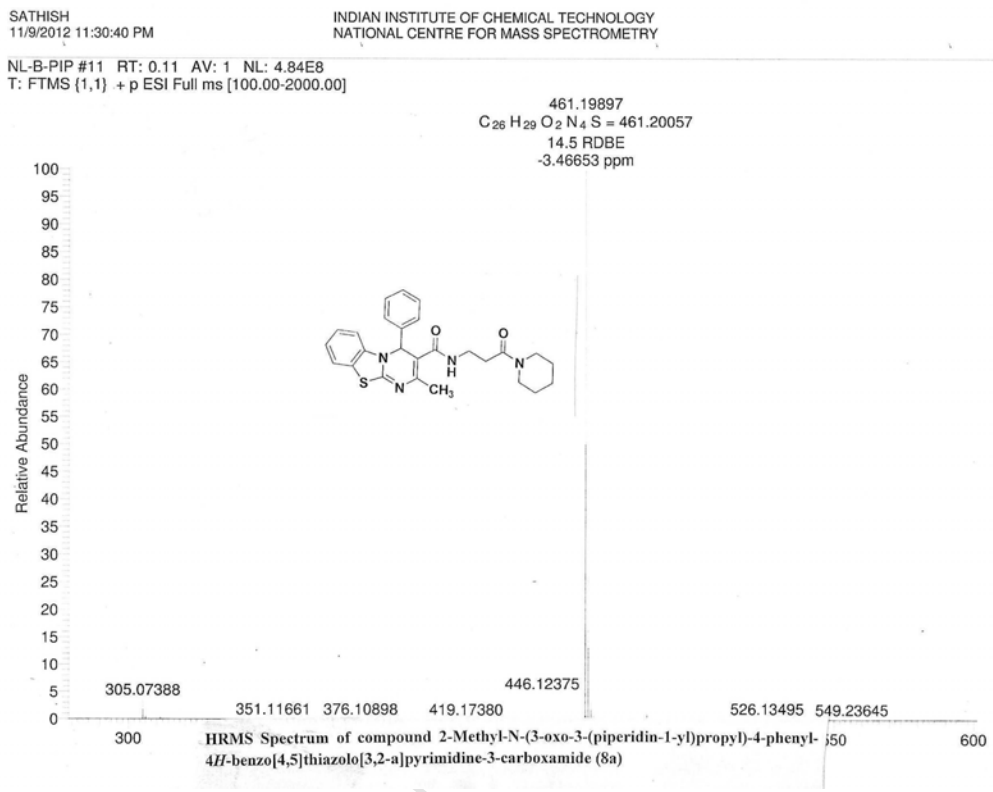
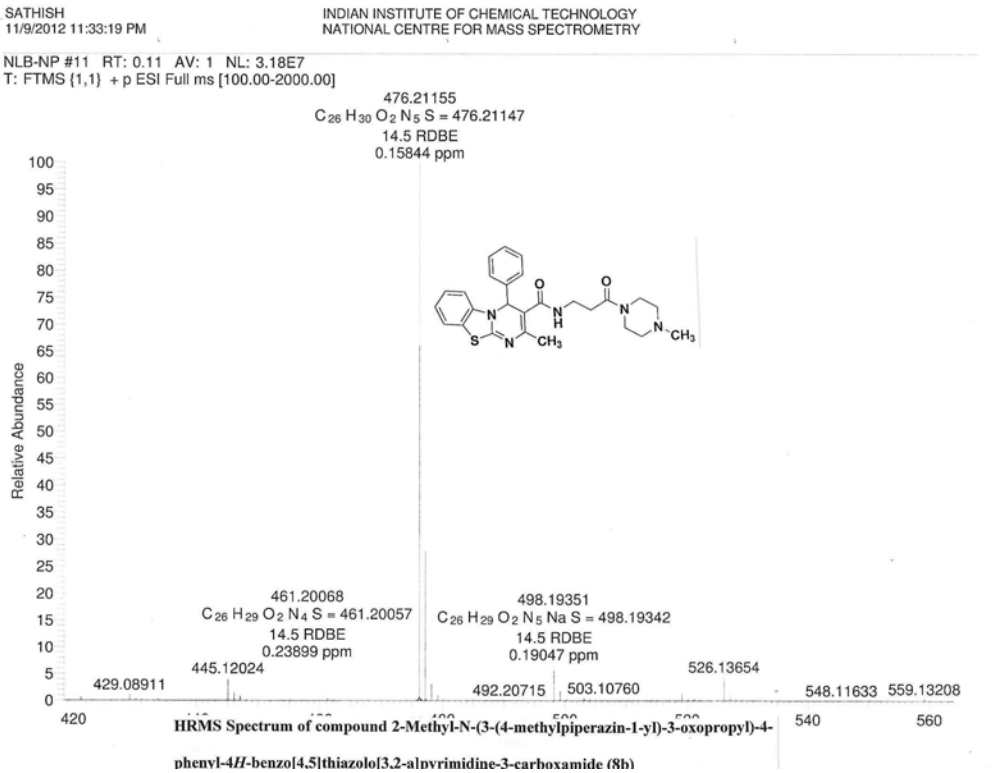


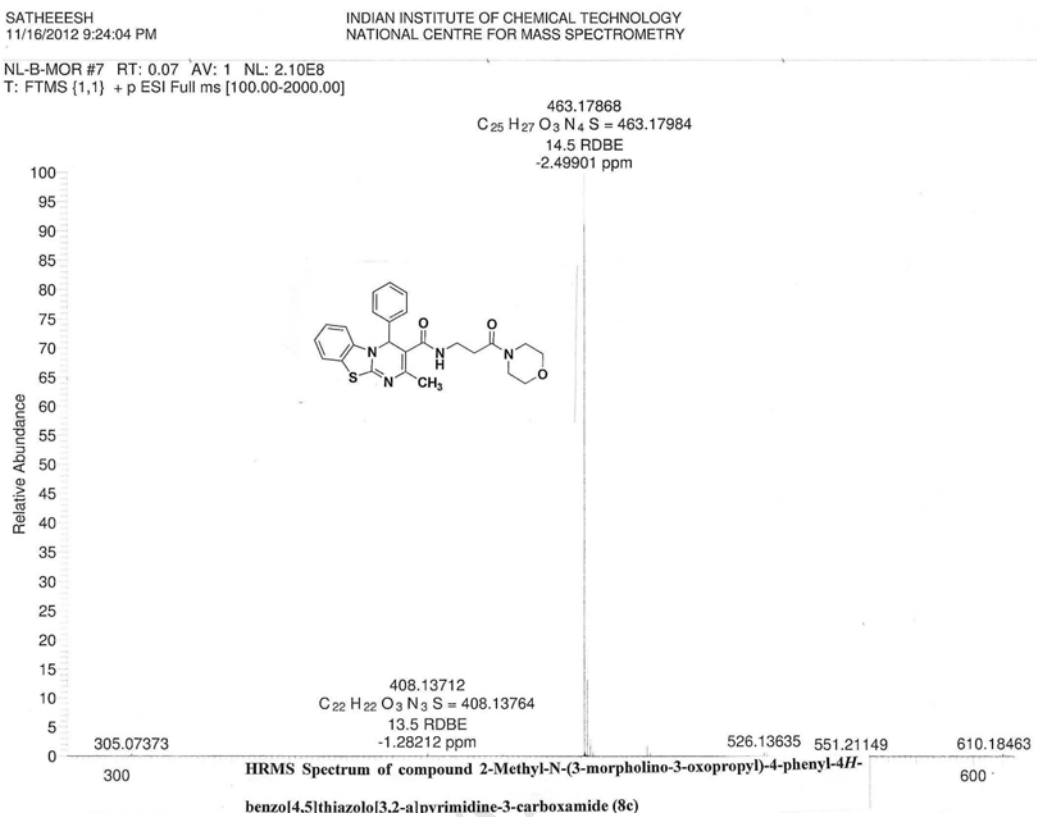
HRMS Spectrum of compound 3-(2-Methyl-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamido) propanoic acid (7)



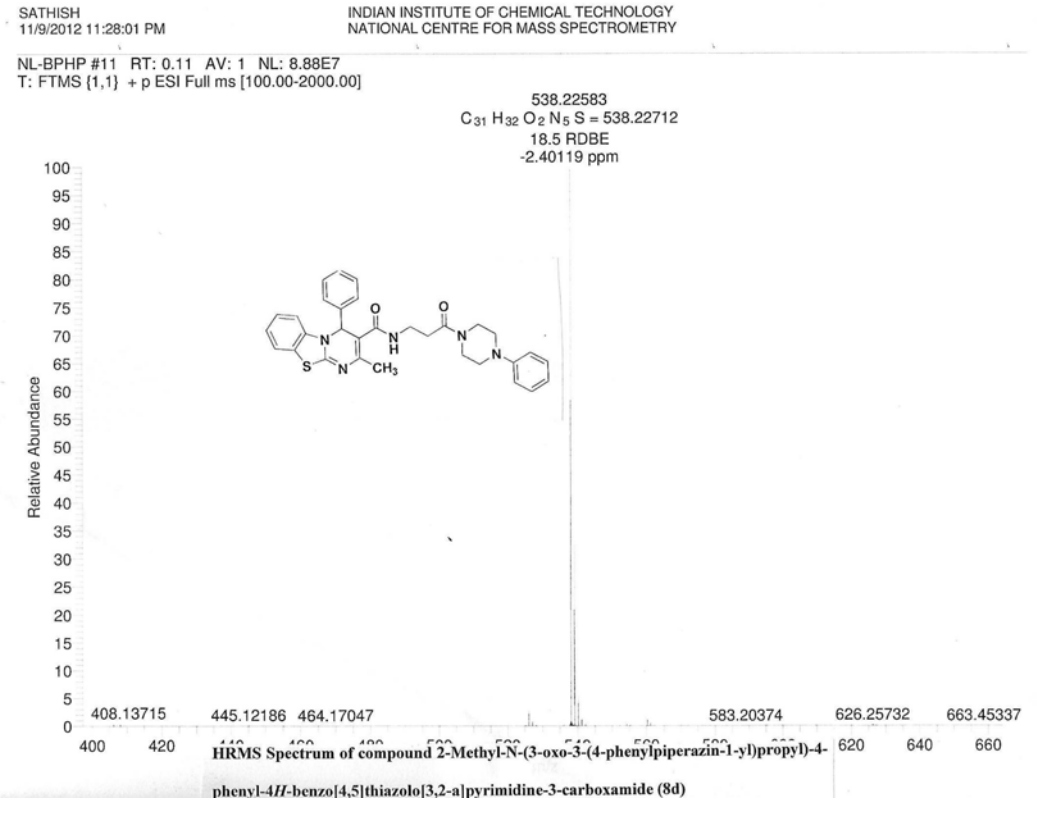
HRMS Spectrum of compound 2-Methyl-N-(3-oxo-3-(piperidin-1-yl)propyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (8a)



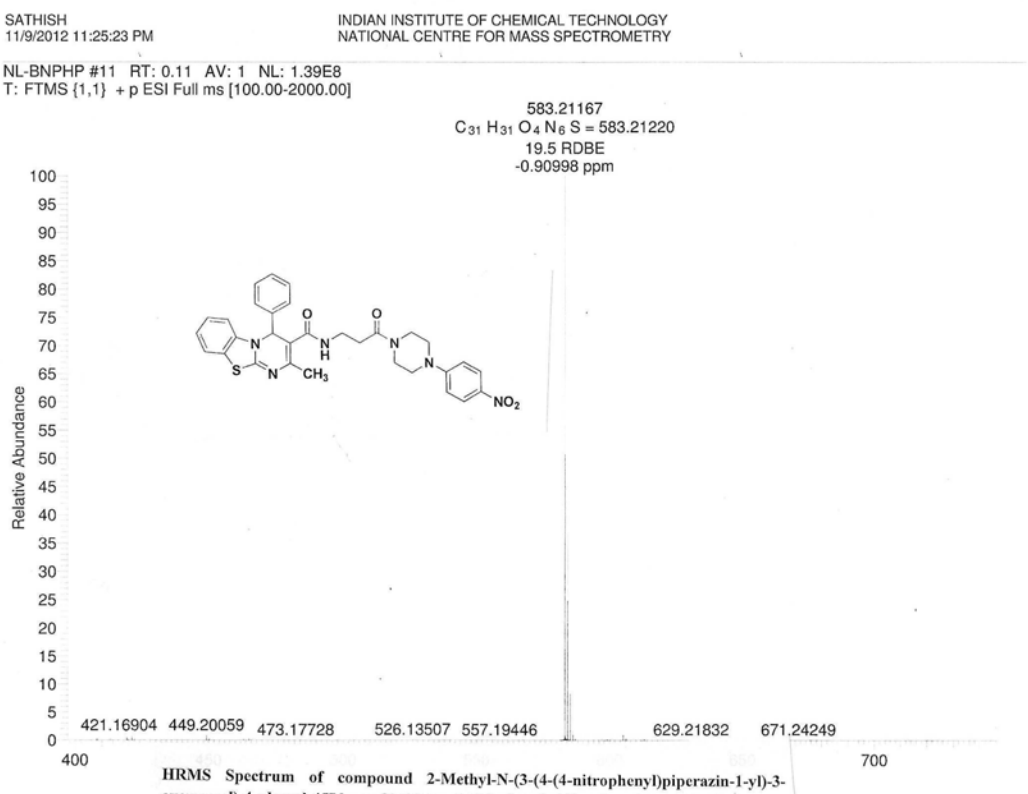
HRMS Spectrum of compound 2-Methyl-N-(3-(4-methylpiperazin-1-yl)-3-oxopropyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (8b)



HRMS Spectrum of compound 2-Methyl-N-(3-morpholino-3-oxopropyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (8c)



HRMS Spectrum of compound 2-Methyl-N-(3-oxo-3-(4-phenylpiperazin-1-yl)propyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (8d)



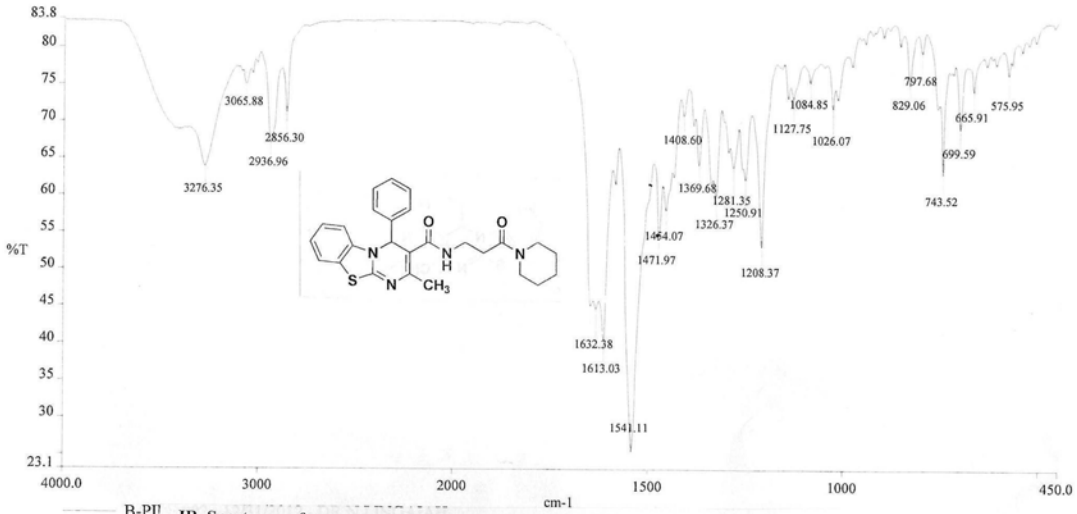
HRMS Spectrum of compound 2-Methyl-N-(3-(4-(4-nitrophenyl)piperazin-1-yl)-3-oxopropyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (8e)

ORGANIC - II, IICT

Description: DR.N.LINGAIAH

Comments

Date: Wednesday, July 17, 2013



B-PI

IR Spectrum of compound 2-Methyl-N-(3-oxo-3-(piperidin-1-yl)propyl)-4-phenyl-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide (8a)