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# Design and synthesis of non-cytotoxic tetrahydrothieno[3,2-*c*]pyridine derivatives exhibiting complement inhibition activity

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A series of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine derivatives have been synthesized and evaluated for their activity on the activation of human complement (classical pathway) and their intrinsic haemolytic activity. The *in vitro* assay results of these analogues for inhibition of complement activity reveals improved inhibitory activity for some of the analogues over existing tetrahydrothienopyridine derivatives like Ticlopidine and Clopidogrel. Significantly, these analogues did not exhibit any haemolytic activity and are non-cytotoxic to human cell lines.

**Keywords**: Tetrahydrothieno[3,2-*c*]pyridine, non-cytotoxic, complement inhibition, haemolysis, classical pathway

Twentieth century has seen extensive research activity with thienopyridine moiety. Several drugs were designed and explored among huge number of synthetic molecules, but only very few of them found clinical use. Tetrahydrothienopyridine derivatives like Ticlopidine and Clopidogrel[1] are among the active molecules in the field of antithrombotic activity currently available in the market.

In the ongoing research activity, dealing with design and synthesis of new complement inhibitors, an attempt has been made to design and synthesize analogues of tetrahydrothieno[3,2-*c*]pyridine and evaluate them for possible clinical application in the field of complement inhibition.

Complement is a vital part of human body's immune system, providing a highly effective means for the destruction of invading microorganisms and for immune complex elimination[2,3]. Clinical and experimental evidence underlines the prominent role of complement in the pathogenesis of numerous inflammatory diseases[4-6], but also organ failure subsequent to ischemia reperfusion injury, sepsis, multiple trauma and burn.

Only recently complement has also been implicated in neurodegenerative disorders such as Alzheimer's disease[7], multiple sclerosis[8] and Guillian-Barre syndrome[9]. The complement system is ubiquitous and is constantly active within living species. The complement system can be activated by and act against, both self and non-self. Under normal conditions, efficient regulation prevents activation against self, however under pathological conditions complement regulation breaks down and activation against self is inevitable[10]. Therefore, it is crucial to develop an array of externally administered therapeutic agents, which would control the various steps of complement activation under condition of cellular stress or disease.

The complement mediated damage can be prevented by specific inhibition of the classical complement pathway without affecting the anti-microbial functions of the complement system *via* the alternative pathway and the lectin pathway[11].

Although several efforts have been made in this direction, there are currently no efficient anti-complement drugs available clinically. A variety of synthetic compounds have been tested for their impact on the complement system, but most of them are either toxic or not complement specific or require unrealistically high concentration to inhibit complement *in vivo*[12].

The current interest in the development of complement inhibitors has emerged due to the involvement of the complement system in several disease processes[12-16].

As part of the efforts to develop new complement inhibitors, low molecular weight analogues were synthesized and their structure-activity relationship (SAR) towards complement inhibition was studied[17,18].

In the present study, an attempt has been made to synthesize derivatives of 4,5,6,7-tetrahydrothieno- [3,2-*c*]pyridine (THTP), a versatile synthon in medicinal chemistry. Various amide derivatives of THTP (**5, 7, 9, 11, 13, 15, 17, 23, 26, 28, 32,** and **35**) with a variety of substituted phenyl and aliphatic moiety were synthesized and their activity was evaluated for the inhibition of activation of human complement (classical pathway). Their intrinsic haemolytic activity on erythrocytes (RBCs) has also been investigated.

The synthetic strategy is outlined in **Schemes I** and **II** (ref. 19).

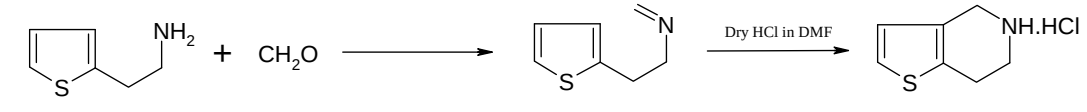
## Results and Discussion

The target compounds **(3, 5, 7, 9, 11, 13, 15, 17, 23, 26, 28, 32,** and **35)** along with Ticlopidine and Clopidogrel were evaluated for their ability to inhibit the *in vitro* activation of human complement (classical pathway) as described earlier[17,20].

The intrinsic haemolytic activity of compounds was also determined by incubating them with sensitized sheep erythrocytes (RBCs) in the absence of complement and monitoring the complement independent lysis.

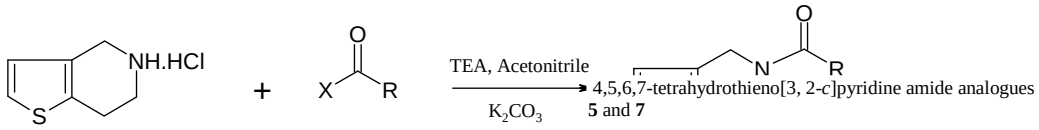
Analogues of THTP.HCl, **3** were tested upto a maximum concentration of 286 μg/mL, using a stock solution of 5 mg/mL in DMSO.

Ursolic acid and oleanolic acid were used as positive controls[17,21]. DMSO was used as vehicle control.



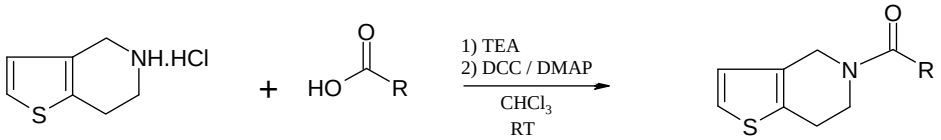

Thiophene-2-ethylamine **1** — Formaldehyde — Formimine Intermediate **2** — 4,5,6,7-Tetrahydrothieno [3, 2-*c*]pyridine.HCl **3**

Synthesis of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride **3**




4,5,6,7-tetrahydrothieno[3, 2-*c*] pyridine.HCl **3** — Acid chloride where X = Cl; RCO = Benzoyl, Cinnamoyl — 4,5,6,7-tetrahydrothieno[3, 2-*c*]pyridine amide analogues **5** and **7**

Method A




4,5,6,7-Tetrahydrothieno[3, 2-*c*] pyridine.HCl **3** — Carboxylic Acid * — 4,5,6,7-tetrahydrothieno[3, 2-*c*]pyridine amide analogues **9, 11, 13, 15, 17, 23, 26, 28, 32** and **35**

* Carboxylic acids RCOOH corresponds to;
Acetic acid **8**; 2-Chlorobenzoic acid **10**; 2-Chlorophenylacetic acid **12**; 2,5-Dichlorobenzoic acid **14**; α-Bromo-α-(2-chloro)phenylacetic acid **16**; 2-Benzyl-2-acrylic acid **22**; 3-Acetylthio-2-benzylpropionic acid **25**; α-Acetamidocinnamic acid **27**; N-(t-Butoxycarbonyl)methionine **30****, 2-Chlorocinnamic acid **34**.

**Amide **31** obtained after reacting compound **30** with THTP, is treated with solution of dry HCl in Methanol to get the final product **32** after deprotection of t-BOC group

Method B

Synthesis of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine amide analogues

**Scheme I** — Synthesis of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine amide analogues

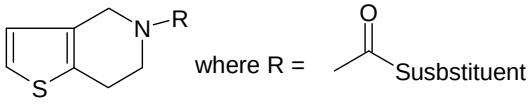
The compounds were also tested for their *in vitro* cytotoxicity against mammalian cell lines (VERO cells: Kidney fibroblast and LLC-PK1: Kidney Epithelial cells) using Neutral Red Assay[22] in a similar way as described earlier[18,23].

The results of complement inhibition activity are reported as $IC_{50}$ values in **Table I**.

As the principal biological role for the complement cascade is the neutralization and removal of invading pathogens, complement system plays an important part in the immune system. However, diseases characterized by excessive or uncontrolled complement activity lead to many inflammatory conditions such as Adult Respiratory Distress Syndrome (ARDS) or myocardial infarction, where, if the pathology is acute then immediate relief of symptoms could be life saving and prevent permanent damage.

The analogues of tetrahydrothienopyridine have been mainly studied for antithrombotic, antiplatelet and anticoagulant activity, which are associated with cardiovascular ailments like ARDS or myocardial infarction[24]. As unwanted complement activity also leads to similar cardiovascular situations as mentioned above, it was thought interesting to explore

**Table I** — Inhibition of complement activity (classical pathway) and haemolytic activity of amide analogues of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (THTP)




| Compd | R | Inhibition of Complement $IC_{50}$ (μM)[a] | Haemolytic activity $EC_{50}$ (μM)[b] | Cytotoxicity $IC_{50}$ (μg/mL) Vero Cells | Cytotoxicity $IC_{50}$ (μg/mL) LLC-$PK_1$ Cells |
|---|---|---|---|---|---|
| **3** | H (THTP.HCl) | NA | NA | NC | NC |
| **5** | Cinnamoyl | 780 | NA | NC | NC |
| **7** | Benzoyl | 494 | NA | NC | NC |
| **9** | Acetyl | >1577 | NA | NC | NC |
| **11** | 2-Chlorobenzoyl | NA | NA | NC | NC |
| **13** | 2-Chlorophenylacetyl | NA | NA | NC | NC |
| **15** | 2,5-Dichlorobenzoyl | 641 | NA | NC | NC |
| **17** | α-Bromo-α-(2-chloro) phenylacetyl | NA | NA | 18.8 | 15 |
| **23** | 2-Benzyl-2-ene propionyl | 636 | NA | NC | NC |
| **26** | 3-Acetylthio-2-benzylpropionyl | 78 | NA | NC | NC |
| **28** | α-Acetamidocinnamoyl | NA | NA | NC | NC |
| **32** | α-Amino-α-methylethyl sulphide acetyl | 407 | NA | NC | NC |
| **35** | 2-Chlorocinnamoyl | 944 | NA | NC | NC |
| **Ticlopidine** | 2-Chlorobenzyl | NA | NA | NC | NC |
| **Clopidogrel** | α-Carboxymethyl-2-chlorobenzyl | NA | NA | NC | NC |
| **Ursolic acid** | - | 54.75 | | | |
| **Oleanolic acid** | - | 79.95 | | | |
| **Doxorubicin**[c] | - | - | - | > 5 | 0.3 |

[a]The concentration of the compound required to inhibit complement mediated haemolysis of sensitized sheep RBCs by 50% compared to vehicle control. $IC_{50}$ values were obtained from dose-response curves of percent inhibition

[b]The concentration of compound effective to cause 50% haemolysis in the absence of complement. Values were obtained from dose-response curves of percent haemolysis

[c]Positive control for cytotoxicity assay

VERO: monkey kidney fibroblasts; LLC-$PK_1$: Pig kidney epithelial cells

The highest concentration tested for cytotoxicity was 25 μg/mL

NC: Non-cytotoxic upto 25 μg/mL

NA: Not active

various analogues of tetrahydrothienopyridine along with Ticlopidine and Clopidogrel, currently available in market.

The study was aimed at understanding whether these compounds could exhibit complement activity, which in turn could also be useful in controlling cardiovascular conditions apart from controlling excessive complement activity.

Since all tetrahydrothienopyridine derivatives including Ticlopidine and Clopidogrel were found to be inactive[25,26] in the *in vitro* assay for antithrombotic activity (antiplatelet aggregation activity) and *in vivo* testing facility for the same was not available with us, only complement inhibition activity studies were carried out as part of this study.

THTP derivatives like Ticlopidine and Clopidogrel involve the condensation of 2-chlorobenzyl and 2-chlorobenzyl substituted with α-carboxymethyl moiety respectively. In the present study, instead of alkyl carbon condensing to THTP part, condensation with carbonyl carbon forming amide linkage was studied. Moreover, various substituents were incorporated on carbonyl carbon starting with simple substitution like methyl, phenyl groups to substituted phenyl rings.

Selection of substituents was random with an idea to generate a range of substituents which may show complement inhibition activity. The *in vitro* assay revealed that THTP.HCl, **3** did not show any complement inhibition activity. Ticlopidine and Clopidogrel also did not exhibit any complement inhibition activity upto a maximum concentration of 286 μg/mL (equivalent to 900 and 1600 μM respectively). THTP.HCl, Ticlopidine and Clopidogrel did not display any haemolytic activity either.

Structural modifications were carried out by incorporating amide linkage instead of alkyl linkage as in Ticlopidine and Clopidogrel and it was interesting to note that when 2-chlorophenyl ring was incorporated, compound **11** did not exhibit any complement inhibition activity. However, when unsubstituted phenyl ring and disubstituted phenyl ring *viz*., 2,5-dichlorophenyl were incorporated, compounds **7** and **15** exhibited complement inhibition with an $IC_{50}$ values of 494 μM and 641 μM respectively. This clearly indicated that there is no significant contribution of 2-chlorophenyl substitution towards the activity owing to structural change.

Appearance of complement inhibition activity by these modifications prompted further investigations and various other substitutions were incorporated to amide linkage and the structure activity relationship was studied.

Methyl substitution (**9**) caused inhibition of complement to <50% at the highest concentration of 286 μg/mL ($IC_{50}$ >1577 μM in **Table I**).

Incorporation of cinnamamide functionality to THTP moiety did not result in as much complement inhibition activity as observed in the case of cinnamic acid functional group in an earlier study[18].

Compound **5** exhibited complement inhibition at $IC_{50}$ of 780 μM. Analogues of cinnamic acid like α-acetamidocinnamic acid on condensation with THTP moiety yielded compound **28** which did not exhibit any activity, while 2-chlorocinnamic acid amide linkage **35** exhibited inhibitory activity with an $IC_{50}$ of 944 μM.

Further, phenyl ring substituted aliphatic acid like derivatives of phenyl acetic acid were also explored.

Incorporation of 2-chlorophenylacetic acid generating compound **13** along with α-bromo substitution (compound **17**) did not exhibit any complement inhibition activity indicating no significant role of 2-chlorophenyl and other halogen substitution on aliphatic acid in making the condensed amide product effective against complement.

To explore amino acid substitution, *dl*-methionine was condensed with THTP generating amide linkage in compound **32** which exhibited complement inhibition activity at 407 μM. These results demonstrate an improvement in activity upon incorporation of amino acid group as compared to other types of substitutions and opens up a new area of amino acid substitution to be explored for designing more potent and specific complement inhibitors.

Similarly, further incorporation of bulkier groups with reactive functional group sites was explored. Condensation of THTP with 2-benzyl-2-acrylic acid resulted in compound **23** that showed an $IC_{50}$ of 636 μM for complement inhibition. This contribution could be affected due to the presence of free olefin on the α-carbon atom to the carbonyl (amide link) carbon atom.

Further, to explore the possibilities of various substitutions on free olefin in compound **23**, one such substitution with thiolacetic acid **24** generating compound **26** was studied. Compound **26** was found to exhibit a potent complement inhibition activity with an $IC_{50}$ of 78 μM and was the most active analog of the series. This further endorses the significance of free olefin group on α-carbon atom which is

improved upon substitution with reactive groups *viz*., thiolacetic acid **24**. This is contrary to the presence of halogen (*viz*., bromide group) on α-carbon atom as in the case of compound **17** which lacked complement inhibition activity.

This study has added significant information in understanding structure-activity relationship for inhibitors of complement activity and the necessary criterion for the selection of relevant functionality in generating analogues of 4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridine.

Significantly, all the compounds (**5, 7, 9, 11, 13, 15, 17, 23, 26, 28, 32** and **5**) including THTP.HCl **3,** Ticlopidine and Clopidogrel did not exhibit any intrinsic haemolytic activity upto the highest concentration tested (286 μg/mL) as determined by incubating them with sensitized sheep erythrocyte (RBCs) in the absence of complement and determining the complement independent lysis of RBCs. Neither of these were cytotoxic to mammalian kidney cell lines up to 25 μg/mL (data not included) thereby confirming their safety and therapeutic potential. Compound **26** with promising complement inhibition activity seems to be a potential candidate molecule for further study.

However, in earlier studies, most of the compounds reported to inhibit complement activity have also been reported to have cytotoxic properties[12-14,21,23].

Further study is warranted to investigate the action of target compound on specific complement inhibition pathways and generation of data on pharmacophore exhibiting complement inhibition activity.

## Experimental Section

All chemicals, reagents and solvents were purchased from commercial sources where available and used as received.

Intermediates were characterized by FTIR, $^1$H NMR and mass spectrometry (MS).

Various methods[27] exists for the synthesis of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine hydrochloride **3**. It may be prepared by partial reduction of thieno[3,2-*c*]pyridine made from various routes[28].

4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridine hydrochloride **3** was prepared as mentioned in patent GB1490050 wherein thiophene-2-ethylamine **1** was reacted with formaldehyde to form formimine **2**. Formimine **2** on reacting with dry HCl in DMF gave a white precipitate of 4,5,6,7-tetrahydrothieno-[3,2-*c*]pyridine hydrochloride (THTP.HCl) **3** in moderate yield (65-70%). Amide analogs of THTP.HCl, **3** were synthesized by known simple reaction[29] using acid chloride *viz*., cinnamoyl chloride **4** and benzoyl chloride **6** in presence of a base in suitable solvent to obtain amide analogues **5-7** in good yields (80-85%). Another convenient method[30] using dicyclohexyldicarbodiimide (DCC)[31] as carboxylic acid activator along with 4-dimethyl-aminopyridine (DMAP)[32] was employed in presence of carboxylic acid *viz*., acetic acid **8**, 2-chlorobenzoic acid **10**, 2-chlorophenyl acetic acid **12**; 2,5-dichloro-benzoic acid **14**, α-bromo-α-(2-chlorophenyl)acetic acid **16**, 2-benzyl-2-acrylic acid **22**, 3-acetyl-2-benzylpropionic acid **25**, α-acetamidocinnamic acid **27**, N-(*t*-butoxycarbonyl)-methionine **30** and 2-chlorocinnamic acid **34** respectively to form amide linkage obtaining amide analogues **9, 11, 13, 15, 17, 23, 26, 28, 32** and **35** in moderate yields.

Subsequently, some of the above mentioned intermediates *viz*., α-bromo-α-(2-chlorophenyl)acetic acid **16,** 2-benzyl-2-acrylic acid **22** (ref. 33), 3-acetylthio-2-benzylpropionic acid **25** (refs 33,34), N-(t-butoxycarbonyl)-methionine **30** (refs 35-37) and 2-chlorocinnamic acid **34** (ref. 38) were also synthesized (**Scheme II**).

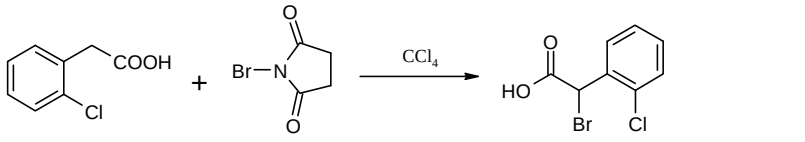
### Synthesis of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine hydrochloride (THTP.HCl, 3)

Thiophene-2-ethylamine **1** (10 g, 0.0813 mole) was heated with 37% aq. formaldehyde (7.25 mL, 0.08943 mole) to yield formamine, which on treatment with dry hydrochloric acid in DMF (6N, 25 mL) yielded THTP.HCl, **3** (6.7 g, 65%). m.p. 220-30°C ; HPLC (Area %): 99.52%. Anal. $C_7H_{10}ClNS$: Found C,47.84; H,5.68; Cl,20.20; N,7.95; S, 18.2. Calcd. C,47.86; H,5.70; Cl,20.23; N,7.98; S, 18.23%. IR (KBr): 3058 (C-H str, aromatic), 2873.7 (C-H str, aliphatic), 1591.7 (C=C asymmetric str), 1497.5, 1459.7 (C=C str, ring), 1215 (C-N str), 979.8 (C-H bending, *trans* olefin), 745.3 cm$^{-1}$ (C-H def, aromatic); $^1$H NMR ($CD_3OD$): δ 3.0-3.7 (m, 4H), 4.2-4.5(s, 2H), 6.8-7.5 (m, 2H); MS: *m/z* 139 ($M^+$ - 36).

### General method for the synthesis of amide analogue (5-7) of THTP.HCl

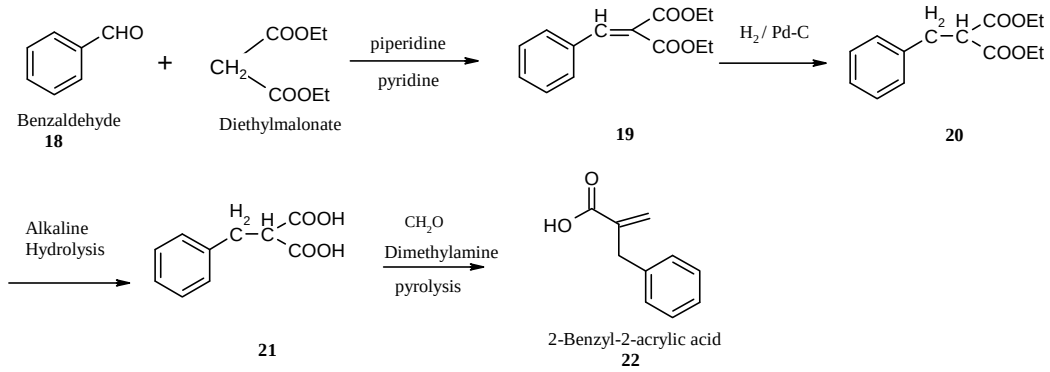
### Method A

4,5,6,7-Tetrahydrothieno(3,2-*c*) pyridine hydrochloride (THTP.HCl, **3**, 1 eq.) was treated with triethylamine (1 eq.) in acetonitrile. Potassium carbonate (1.25 eq.) was added to it and stirred. Acid chloride (**4** and **6**, 1 eq.) was added to it maintaining



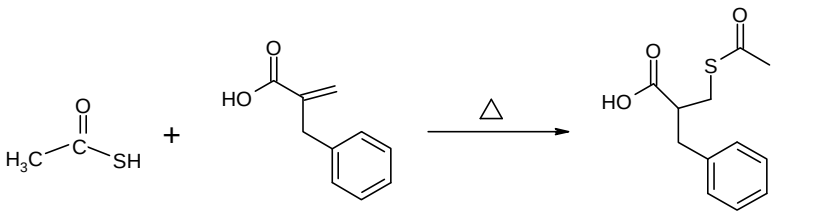

2-Chlorophenylacetic acid **12** | N-Bromosuccinimide | α-Bromo-α-(2-chlorophenyl)acetic acid **16**

Synthesis of α-Bromo-α-(2-chlorophenyl)acetic acid **16**



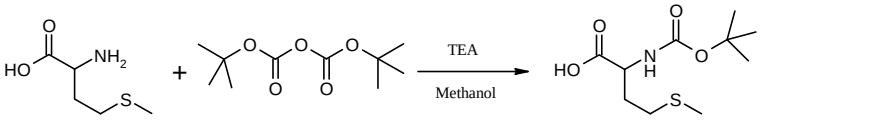

Benzaldehyde **18** | Diethylmalonate | **19** | **20** | **21** | 2-Benzyl-2-acrylic acid **22**

Synthesis of 2-Benzyl-2-acrylic acid **22**



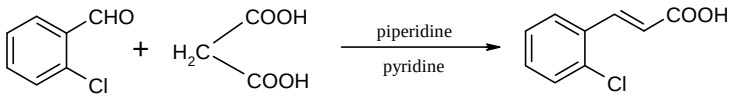

Thiolacetic acid **24** | 2-benzyl-2-acrylic acid **22** | 3-acetylthio-2-benzyl propionic acid **25**

Synthesis of 3-acetylthio-2-benzylpropionic acid **25**




*dl*-Methionine **29** | Di-*tert*-butyldicarbonate(*t*-BOC) | N-(*t*-Butoxycarbonyl)-methionine **30**

Synthesis of N-(*t*-butoxycarbonyl)methionine **30**




2-Chlorobenzaldehyde **33** | Malonic acid | 2-Chlorocinnamic acid **34**

Synthesis of 2-chlorocinnamic acid **34**

Intermediates used in **Scheme I**

**Scheme II** — Synthesis of 2-chlorocinnamic acid **34** from intermediates used in **Scheme I**

reaction temperature. After completion of addition, reaction temperature was gradually raised to RT and subsequently heated to reflux for 4-5 hr to obtain the desired product (**5** and **7**) in good yield (80-85%).

**4, 5, 6, 7-Tetrahydrothieno(3,2-*c*)pyridine-5-cinnamamide, 5** m.p. 170-74°C; GC (Area %): 100.0%. Anal. $C_{16}H_{15}NOS$: Found C,71.32; H,5.54; N,5.18; S, 11.86. Calcd. C,71.38; H,5.58; N,5.20; S, 11.90%. IR (KBr): 3058 (C-H str, aromatic), 2873.7 (C-H str, aliphatic), 1643 (C=O str. amide), 1591.7 (C=C asymmetric str), 1612, 1497.5, 1459.7 (C=C str, ring), 1215 (C-N str), 979.8 (C-H bending, *trans* olefin), 745.3 $cm^{-1}$ (C-H def, aromatic); $^1H$ NMR ($CDCl_3$): δ 2.8-3.2 (t, 2H), 3.8-4.2 (m, 2H), 4.8 (s, 2H), 6.6-6.9 (d, 1H), 6.9-7.2(d, 1H); 7.2-8.0 (m, 7H); MS: *m/z* 269 ($M^+$).

**4,5,6,7-Tetrahydrothieno(3,2-*c*)pyridine-5-benzamide, 7** GC (Area %): 100.0% (Oily product). Anal. $C_{14}H_{13}NOS$: Found C,69.11; H,5.32; N,5.72; S, 13.13. Calcd. C,69.14; H,5.35; N,5.76; S, 13.17%. IR ($CHCl_3$): 3061.3 (C-H str, aromatic), 2926.4 (C-H str, aliphatic), 1633 (C=O str. amide), 1492.9, 1430.7 (C=C str, ring), 1217 (C-N str), 750 $cm^{-1}$ (C-H def., aromatic); $^1H$ NMR ($CDCl_3$): δ 2.6-3.3 (t, 2H), 3.4-4.1 (m, 2H), 4.7(4.5-5.0) (s, 2H), 7.0-7.7 (m, 7H); MS: *m/z* 243 ($M^+$).

**General method for the synthesis of amide analogue (9, 11, 13, 15, 17, 23, 26, 28, 32 and 35) of THTP.HCl**

**Method B**

4,5,6,7-Tetrahydrothieno(3,2-*c*)pyridine hydrochloride (THTP.HCl, **3**, 1 eq.) was treated with triethylamine (1 eq.) in chloroform to obtain the free base. Dicyclohexyldicarbodiimide (DCC, 1 eq.) and 4-dimethylaminopyridine (DMAP, 0.1 eq.) was added to it followed by the desired carboxylic acid (**8, 10, 12, 14, 16, 22, 25, 27, 30** and **34**) (1 eq.) to obtain the product in good yield (55-60%).

Compound **32** was obtained after deprotection of *t*-BOC derivative of the amide **31** (obtained after reaction with *t*-BOC amino acid **30**).

**4,5,6,7-Tetrahydrothieno(3,2-*c*)pyridine-5-acetamide, 9** m.p. 145-50°C ; GC (Area %): 99.47%. Anal. $C_9H_{11}NOS$: Found C,59.65; H,6.07; N,7.71; S, 17.64. Calcd. C,59.67; H,6.08; N,7.73; S, 17.68%. IR (KBr): 3009 (C-H str, aromatic), 2935 (C-H str, aliphatic), 1635.6 (C=O str. amide), 1438 (C=C str, ring), 1371 (C-H def., alkane -$CH_3$), 1216 $cm^{-1}$ (C-N str); $^1H$ NMR ($CDCl_3$): δ 1.6-2.2 (s, 3H), 2.5-3.4 (t, 2H), 3.4-4.2 (m, 2H), 4.6(4.2-4.8) (s, 2H), 6.3-7.4 (m, 2H); MS: *m/z* 181 ($M^+$).

**4, 5, 6, 7-Tetrahydrothieno(3, 2-*c*)pyridine-5-(2-chloro)benzamide, 11** m.p. 182-84°C ; GC (Area %): 99.49%. Anal. $C_{14}H_{12}ClNOS$: Found C,60.53; H,4.31; Cl, 12.75; N,5.03; S, 11.52. Calcd. C,60.54; H,4.32; Cl, 12.79; N,5.05; S, 11.53%. IR (KBr): 3010 (C-H str, aromatic), 2938, 2854 (C-H str, aliphatic), 1633 (C=O str. amide), 1430 (C=C str, ring), 1218 (C-N str), 831 (C-H def), 706 $cm^{-1}$ (C-Cl str); $^1H$ NMR ($CDCl_3$): δ 2.6-3.2 (t, 2H), 3.3-3.8 (m, 2H), 4.4 (3.8-4.6) (s, 2H), 6.4-8.0 (m, 6H); MS: *m/z* 277 ($M^+$).

**4,5,6,7-Tetrahydrothieno(3,2-*c*)pyridine-5-(2-chlorophenyl)acetamide, 13** m.p. 192-96°C; GC (Area %): 99.67%. Anal. $C_{15}H_{14}ClNOS$: Found C,61.73; H,4.8; Cl, 12.15; N,4.78; S, 10.98. Calcd. C, 61.75; H, 4.80; Cl, 12.18; N, 4.80; S, 10.98%. IR (KBr): 3019 (C-H str, aromatic), 2969, 2852 (C-H str, aliphatic), 1643 (C=O str. amide), 1445.7 (C=C str, ring), 1226.4 (C-N str), 706 $cm^{-1}$ (C-Cl str); $^1H$ NMR ($CDCl_3$): δ 2.5-3.2 (t, 2H), 3.5-4.2 (m, 2H), 3.9-4.0 (s, 2H), 4.3-4.8 (s, 2H), 6.4-7.5 (m, 6H); MS: m/z 291 ($M^+$).

**4,5,6,7-Tetrahydrothieno (3,2-*c*)pyridine-5-(2,5-dichloro)benzamide, 15** m.p. 189-90°C; GC (Area %): 99.62%. Anal. $C_{14}H_{11}Cl_2NOS$: Found C,53.83; H,3.52; Cl,22.75; N,4.48; S,10.26. Calcd. C,53.85; H,3.53; Cl,22.76; N,4.49; S,10.026%. IR (KBr): 3009 (C-H str, aromatic), 2936, 2857 (C-H str, aliphatic), 1638 (C=O str. amide), 1439 (C=C str, ring), 1223 (C-N str), 761 (C-H def.), 671 $cm^{-1}$ (C-Cl str); $^1H$ NMR ($CDCl_3$): δ 2.7-3.2 (t, 2H), 3.2-3.9 (m, 2H), 4.4 (4.2-4.5) (s, 2H), 6.5-7.6 (m, 5H); MS: *m/z* 313 ($M^+$).

**4, 5, 6, 7-Tetrahydrothieno(3, 2-*c*)pyridine-5-(α-bromo-α-(2-chlorophenyl))acetamide, 17** m.p. 210-15°C; GC (Area %): 99.80%. Anal. $C_{15}H_{12}BrClNOS$: Found C,48.71; H,3.22; Br,21.62; Cl,9.6; N,3.76; S,8.62. Calcd. C,48.73; H,3.25; Br,21.63; Cl,9.61; N,3.79; S,8.66%. IR (KBr): 3015 (C-H str, aromatic), 2846 (C-H str, aliphatic), 1655.5 (C=O str. amide), 1566, 1429 (C=C str, ring), 1217 (C-N str), 610 $cm^{-1}$ (C-Br str); $^1H$ NMR ($CDCl_3$): δ 2.5-3.1 (t, 2H), 3.6-4.2 (m, 2H), 4.7 (4.3-4) (s, 2H), 6.2 (6.1-6.3) (s, 1H), 6.9-7.5 (m, 6H); MS: *m/z* 369 ($M^+$).

**4, 5, 6, 7-Tetrahydrothieno(3, 2-*c*)pyridine-5-(2-benzyl-2-ene)propionamide, 23** m.p. 188-92°C; GC (Area %): 99.98%. Anal. $C_{17}H_{17}NOS$: Found C,72.05; H,6.0; N,4.94; S,11.3. Calcd. C,72.08; H,6.01; N,4.95; S,11.31%. IR (KBr): 3009 (C-H str, aromatic), 2935, 2853 (C-H str, aliphatic), 1634 (C=O str. amide), 1612 (C=C str, terminal olefin), 1510,

1466, 1441 (C=C str, ring), 1254 (C-N str), 937 $cm^{-1}$ (C-H def., olefin); $^1H$ NMR ($CDCl_3$): δ 2.3-2.9 (t, 2H), 3.2-4.0 (m, 2H), 3.7 (s, 2H), 4.5(4.2-4.8) (s, 2H), 5.0-5.4 (d, 2H, terminal olefin), 6.2-7.6 (m, 7H); MS: *m/z* 283 ($M^+$).

**4,5,6,7-Tetrahydrothieno(3,2-*c*)pyridine-5-(3-acetylthio-2-benzyl) propionamide, 26** GC (Area %): 99.14% (viscous liquid). Anal. $C_{19}H_{21}NO_2S_2$: Found C,63.5; H,5.83; N,3.88; S,17.82. Calcd. C,63.51; H,5.85; N,3.90; S,17.83%. IR ($CHCl_3$): 3064 (C-H str, aromatic), 2926 (C-H str, aliphatic), 1643.4 (C=O str. amide), 1434.7 (C=C str, ring), 1225 (C-N str), 750 (C-H def., aromatic), 620 $cm^{-1}$ (C-S str); $^1H$ NMR ($CDCl_3$): δ 2.1-2.5 (d, 4H), 2.5-3.1 (t, 2H), 3.1-3.6 (m, 2H), 3.2 (s, 3H), 3.6-4.0 (m, 1H), 4.6(4.4-4.8) (s, 2H), 6.4-7.5 (m, 7H); MS: *m/z* 359 ($M^+$).

**4,5,6,7-Tetrahydrothieno(3,2-*c*)pyridine-5-(α-acetamido)cinnamamide, 28** m.p. 147-49°C; GC (Area %): 99.84%. Anal. $C_{18}H_{18}N_2O_2S$: Found C,66.25; H,5.51; N,8.55; S,9.79. Calcd. C,66.26; H,5.52; N,8.59; S,9.82%. IR (KBr): 3416 (N-H str), 3010 (C-H str, aromatic), 2936 (C-H str, aliphatic), 1685, 1628 (C=O str. amide), 1591 (C=C str, asymmetric), 1473, 1438 (C=C str, ring), 1370 (C-H def., alkane), 1237, 1207 (C-N str), 1050 (C-H def., *trans* olefin), 790 $cm^{-1}$ (C-H def, trisubstituted alkene); $^1H$ NMR ($CDCl_3$): δ 1.8-2.3 (s, 3H), 2.7-3.1 (t, 2H), 3.7-4.2 (m, 2H), 4.7(4.3-4.9) (s, 2H), 5.7-6.0 (s, 1H), 6.6-7.8 (m, 7H); MS: *m/z* 326 ($M^+$).

**4,5,6,7-Tetrahydrothieno(3,2-*c*)pyridine-5-(α-amino-α-methylethylsulphide)acetamide, 32** GC (Area %): 99.91% (viscous liquid). Anal. $C_{12}H_{18}N_2OS_2$: Found C, 53.31; H, 6.64; N, 10.38; S, 23.68. Calcd. C, 53.33; H, 6.67; N, 10.37; S, 23.70%. IR ($CHCl_3$): 3383 (C-H str, aromatic), 3050, 2921, 2855 (C-H str, aliphatic), 1631.9 (C=O str. amide), 1438 (C=C str, ring), 1226.9 (C-N str), 826 $cm^{-1}$ (C-H def., aromatic); $^1H$ NMR ($CDCl_3$): δ 1.1-1.6 (q, 2H), 1.6-2.4 (t, 2H), 2.2(2.1-2.3) (s, 3H), 2.4-3.2 (t, 2H), 3.4-4.3 (m, 3H), 4.7( 4.5-4.9) (s, 2H), 6.6-7.3 (m, 2H); MS: *m/z* 270 ($M^+$).

**4, 5, 6, 7-Tetrahydrothieno(3, 2-*c*)pyridine-5-(2-chloro)cinnamamide, 35** m.p.186-89°C; GC (Area %): 99.52%. Anal. $C_{16}H_{14}ClNOS$: Found C,63.24; H,4.59; Cl,11.69; N,4.59; S,10.52. Calcd. C,63.26; H,4.61; Cl,11.70; N,4.61; S,10.54%. IR (KBr): 3010 (C-H str, aromatic), 2934, 2854 (C-H str, aliphatic), 1646 (C=O str. amide), 1609 (C=C str, olefin), 1472, 1433 (C=C str, ring), 1224 (C-N str), 973 (C-H def., disubstituted alkene, *trans*), 790 $cm^{-1}$ (C-H def., aromatic); $^1H$ NMR ($CDCl_3$): δ 2.7-3.2 (t, 2H), 3.7-4.2 (m, 2H), 4.7(4.6-5.0) (s, 2H), 6.6-7.2 (2d, 2H, olefin), 7.1-7.8 (m, 6H); MS: *m/z* 303 ($M^+$).

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