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DESIGN, SYNTHESIS AND SPECTROSCOPIC CHARACTERIZATION OF SOME NEW HYBRID MOLECULES CONSISTING DIARYLSULFONYLUREA AND CHALCONE MOIETIES

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ABSTRACT

As a part of our research investigation aimed at search for new hybrid pharmacophores as potential cytotoxic, antidiabetic and antimicrobial agents, we are interested to have α,β-unsaturatedketone linker to the diarylsulfonylurea basic nucleus to give a series of diarylsulfonylurea-chalcone conjugates. Therefore, in the present study an attempt has been made to conventionally synthesize and characterize some new diarylsulfonylurea-chalcone conjugates of 1-(2-acetyl-3-pyridinyl)-3-tosylurea (I) by reaction with various aromatic/ heteroaromatic aldehydes. All the structures of the diarylsulfonylurea-chalcone conjugates were appropriately established by IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopic and analytical data.

Key words: new hybrid pharmacophores, diarylsulfonylurea-chalcone

INTRODUCTION

Diarylsulfonylureas are the structural analogs of urea (NH_2CONH_2) with aromatic sulfonyl group in the position 3 and an aromatic or heteroaromatic ring at the position 1. Diarylsulfonylureas became widely available since 1955 as popular antidiabetic drugs in clinical practice for the treatment of type 2 diabetes, by virtue of their insulin secretagogue properties. The synthesis of compounds containing diarylsulfonylurea moiety has been a subject of extensive research in the recent past because of their enormous biological activities such as hypoglycemics [1-4], *Vibrio fischeri* quorum sensing regulators [5], CXCR2 receptor antagonists [6], antimalarials [7], antibacterials [8], human thromboxane A_2 receptor isoforms TP_α and TP_β antagonists [9], reversible inhibitors of human steroid sulfatase [10], K_{ATP}-channel openers [11], ANG II (AT_1) receptor antagonists [12], oncolytics [13], acyl-CoA inhibitors [14], vasodilators [15], aldehyde dehydrogenase inhibitors [16], cancer chemotherapeutics [17], diuretic [18], β_3 adrenergic receptor agonists [19]

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Non competitive inhibitors of acetohydroxyacid synthase from *Mycobacterium tuberculosis* [20], and as peroxisome proliferator activated receptor gamma (PPARγ) agonists [21]. Similarly, chalcones (α,β-unsatured ketones) have also been gained huge significance as these compounds exhibit several biological activities, such as antimicrobial [22], antiviral [23], antioxidant [24], radical inhibitor [25], antitumor [26], carbonic anhydrase inhibitor [27], xanthine oxidase inhibitor [28], antibacterial [29], plant growth regulator [30], free radical scavenger [31], anti-inflammatory [32] and analgesic [33]. These activities are largely attributed due to the α,β-unsatured ketone moiety [34]. Consequently a number of strategies have been originated to synthesize them [35-37]. Based on the above observations, an attempt has been made in the present study to combine these two bioactive pharmacophores in a single molecular platform through molecular hybridization strategies. Hence, it was considered worthwhile to synthesize and characterize some novel diarylsulfonylurea-chalcone hybrids (II.1-28) in the present study [38]. To the best of our knowledge there is, to date, no reports have been published on the synthesis and characterization of the proposed compounds.

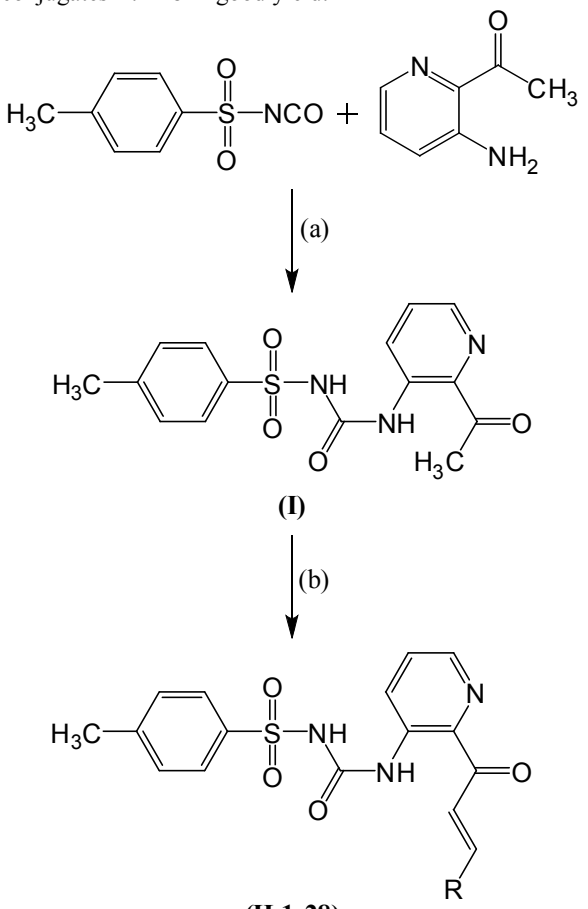
EXPERIMENTAL

INSTRUMENTATION

Melting points were taken in open capillary tubes and are therefore uncorrected. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using *n*-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an iodine chamber. The FT-IR spectra were recorded on Perkin-Elmer spectrometer. The ^{1}H NMR spectra were scanned on a Bruker 400 MHz. spectrometer in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm. The ESI mass spectra were recorded on an Agilent 6100 QQQ spectrometer.

CHEMISTRY

The reaction sequence employed in the synthesis of diarylsulfonylurea-chalcone conjugates (II.1-28) is shown in Scheme 1, and their physical properties are depicted individually. The key intermediate in the present study 1-(2-acetyl-3-pyridinyl)-3-tosylurea (I) was synthesized by reaction of tosylisocyanate with 2-acetyl-3-aminopyridine and subsequent Claisen-Schmidt condensation of the intermediate (I) with appropriate aromatic/heteroaromatic aldehydes under basic conditions to give the corresponding diarylsulfonylurea-chalcone conjugates II.1-28 in good yield.



Scheme 1. Reagents and conditions: (a) Dry DCM (CH_2Cl_2), reflux, 30 min; (b) Ethanol, 100% aq. KOH solution, substituted aromatic/heteroaromatic aldehydes.

RESULTS AND DISCUSSION

General procedure for the synthesis of 1-(2-acetyl-3-pyridinyl)-3-tosylurea (I)

To a solution of 2-acetyl-3-aminopyridine (0.01 M) dissolved in 20 mL of dry dichloromethane (CH_2Cl_2), tosyl isocyanate (0.015 M) was added quickly by delivering through a syringe and the resulting mixture was stirred at room temperature for 10 min, the reaction mixture was then heated under reflux for 30 min and then cooled or evaporated to isolate the product. The crude 1-(2-acetyl-3-pyridinyl)-3-tosylurea **(I)** was washed on the vaccum filter with cold dichloromethane and then recrystallized from ethanol.

General procedure for the synthesis of diarylsulfonylurea-chalcone conjugates (II.1.28)

To a solution of 1-(2-acetyl-3-pyridinyl)-3-tosylurea (**I**) (0.005 M) and suitably substituted aldehydes (0.005 M) in ethanol (10 ml), aqueous solution of potassium hydroxide (100%) was added drop wise with continuous stirring at room temperature over a period of 10 min. The reaction mixture was then kept at room temperature for about 48 h with occasional shaking. After 48 h it was poured into ice-cold water, and then neutralized to pH 2 using 5 N hydrochloric acid. The yellow precipitate obtained was filtered, washed, dried, and recrystallized from dry ethanol. The diarylsulfonylurea-chalcone conjugates **II.1-28** were obtained in good yield. All the synthesized compounds as mentioned in **Table 5.1** were characterized by spectroscopic methods such as FTIR, ^{1}H NMR, ^{13}C NMR and LC mass spectral analysis.

Synthesis of *(E)*-1-[2-(3-(phenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.1)

A mixture of 1-(2-acetylphenyl)-3-tosylurea (**I**) (0.005 mol.) and benzaldehyde (0.005 mol.) was stirred in ethanol (7.5 mL) and then an aqueous solution of KOH (100%, 7.5 mL) was added to it. The mixture was kept for 48 h and it was acidified with 1:1 HCl and H_2O. Then it was filtered under vacuum and the solid was washed with water, purified by column chromatography and crystallized from a mixture of ethanol and water (1:1). Compound **II.1**, analyzed for $C_{22}H_{19}N_3O_4S$, m.p. 123 ^oC. The IR spectrum **(Fig. 5.4)** of compound **II.1** exhibited the characteristic absorption bands at 3500- 3200 cm^{-1} and 1650-1715 cm^{-1} suggesting the presence of a secondary amine group and α,β-unsaturated carbonyl group respectively. The CH_3 group in the *para* position to the SO_2–N--, was shown by a strong band at 817 cm^{-1} region. Bands attributed to the presence of sulfonyl (–SO_2–) symmetrical and unsymmetrical stretches were observed at 1120 cm^{-1} and 1300 cm^{-1} respectively. The 400 MHz ^{1}H-NMR spectrum **(Fig. 5.2)** of the compound **II.1** in DMSO-d_6 with TMS as an internal standard exhibited characteristic peaks of H-α and H-β protons of α,β-unsaturated carbonyl group as two doublets, one at δ 7.96 ppm (H-β, J=15.6 Hz) and the other one at δ 7.65 ppm (H-α, J=15.6 Hz). The large J value clearly reveals the *trans* geometry at the double bond. In the ^{13}C-NMR spectrum **(Fig. 5.3)** a carbonyl carbon **(II.1)** appeared at δ

192.6 ppm. The α and β carbon atoms with respect to the carbonyl group showed characteristic signals at δ 125.9 ppm (C_α) and δ 145.6 ppm (C_β) respectively. The ESI mass spectrum **(Fig. 5.4)** of compound **II.1** revealed a molecular ion at *m/z* 421. Eventually all the spectra of the new products are in keeping with the expected structures. The results of elemental analysis were also in close agreement with those of the calculated values. Based on the above spectral data and elemental analysis, the structure of the compound was confirmed as *(E)*-1-[2-(3-(phenyl) acryloyl)-3-pyridinyl]-3-tosylurea **(II.1).** By adopting the above the synthetic procedure, diarylsulfonylurea-chalcone conjugates **(II.1-28)** were also synthesized. All these compounds are new and the characteristic physical and spectral data were presented individually as follows.

(E)-1-[2-(3-(tolyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.2)

Yield: 89%; yellow powder; m.p.147 ^oC; IR (KBr, ν_{max} cm^{-1}): 1298.71 (SO_2, asymmetrical), 1182.04 (SO_2, symmetrical), 3317.84, 3428.12 (N−H), 1645.58 (C=O), 1616.05 (C=C), 3073.99 (C–H), 1575.86 (CONH), 1337.17 (C-N), 1542.03 (N-H bend) ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 7.17-7.38 (m, 10H, Ar-H), 7.42 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.62 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.91 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 8.07 (d, *J* = 8.1 Hz, 2H, Ar-H), 10.33 (s, 1H, NH), 11.73 (s, 1H, NH); ESI-MS (*m/z*): 436 $[M]^+$; Anal. Calcd. for $C_{23}H_{21}N_3O_4S$, %: C, 66.34; H, 5.10; N, 6.45; Found, %: C, 66.32; H, 5.13; N, 6.55.

(E)-1-[2-(3-(4-*N*,*N*-dimethylaminophenyl)acryloyl)-3-pyridinyl]-3-tosylurea (II.3)

Yield: 88%; yellow powder; m.p. 158 ^oC; IR (KBr, ν_{max} cm^{-1}): 1310.93 (SO_2, asymmetrical), 1156.47 (SO_2, symmetrical), 3460.79 (N−H), 3341.88 (C=O), 1651.93 (C=C), 3038.58 (C–H), 1591.18 (CONH), 1353.15 (C-N), 1531.71 (N-H bend) ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 2.38 (s, 6H, CH_3), 7.36-7.77 (m, 4H, Ar-H), 7.43 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.69 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.84 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 8.01 (d, *J* = 8.1 Hz, 2H, Ar-H), 10.89 (s, 1H, NH), 12.02 (s, 1H, NH); ESI-MS (*m/z*): 465 $[M]^+$; Anal. Calcd. for $C_{24}H_{24}N_4O_4S$, %: C, 64.78; H, 5.44; N, 9.06; Found, %: C, 64.71; H, 5.25; N, 9.11.

(E)-1-[2-(3-(3-methoxyphenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.4)

Yield: 95%; yellow powder; m.p. 146 ^oC; IR (KBr, ν_{max} cm^{-1}): 1262.45 (SO_2, asymmetrical), 1152.05 (SO_2, symmetrical), 3238.57 (N−H), 1729.59 (C=O), 1700.13 (C=C), 3068.90 (C–H), 1578.27 (CONH), 1338.21 (C-N), 1520.40 (N-H bend) ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.43 (d, *J* = 8.1 Hz, 2H, Ar-H),7.45-7.86 (m, 7H, Ar-H), 7.69 (d, *J* = 15.4 Hz, 1H, HC=CH (H-α)), 7.87 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.97 (d, *J* = 15.4 Hz, 1H, HC=CH (H-β)), 9.01 (s, 1H, NH), 11.99 (s, 1H, NH); ESI-MS (*m/z*): 452$[M]^+$; Anal. Calcd. for $C_{23}H_{21}N_3O_5S$, %: C, 63.98; H, 4.92; N, 6.22; Found, %: C, 63.66; H, 4.72; N, 6.23.

(E)-1-[2-(3-(4-methoxyphenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.5)

Yield: 81%; yellow powder; m.p. 199 ^oC; IR (KBr, ν_{max} cm^{-1}): 1304.33 (SO_2, asymmetrical), 1174.29 (SO_2, symmetrical), 3451.08, 3331.11 (N−H), 1645.56 (C=O), 1630.23 (C=C), 3035.49 (C–H), 1598.83 (CONH), 1335.79 (C-N), 1572.43 (N-H bend) ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.25-7.66 (m, 7H, Ar-H), 7.42 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.68 (d, *J* = 15.4 Hz, 1H, HC=CH (H-α)), 7.85 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.91 (d, *J* = 15.4 Hz, 1H, HC=CH (H-β)), 11.03 (s, 1H, NH), 12.33 (s, 1H, NH); ESI-MS (*m/z*):452 $[M]^+$; Anal. Calcd. for $C_{23}H_{21}N_3O_5S$, %: C, 63.98; H, 4.92; N, 6.22; Found, %: C, 63.97; H, 4.85; N, 6.34.

(E)-1-[2-(3-(3,4-dimethoxyphenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.6)

Yield: 85%; yellow powder; m.p. 188 ^oC; IR (KBr, ν_{max} cm^{-1}): 1311.69 (SO_2, asymmetrical), 1153.99 (SO_2, symmetrical), 3224.98 (N−H), 1716.60 (C=O), 1655.77 (C=C), 2838.23 (C–H), 1592.33 (CONH), 1341.34 (C-N), 1524.60 (N-H bend); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 3.88 (s, 9H, OCH_3), 7.38-7.61 (m, 3H, Ar-H), 7.42 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.67 (d, *J* = 15.4 Hz, 1H, HC=CH (H-α)), 7.83 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.89 (d, *J* = 15.4 Hz, 1H, HC=CH (H-β)), 10.43 (s, 1H, NH); 11.99 (s, 1H, NH); ESI-MS (*m/z*): 482 $[M]^+$; Anal. Calcd. for $C_{24}H_{23}N_3O_6S$, %: C, 62.49; H, 5.03; N, 5.83; Found, %: C, 62.17; H, 5.12; N, 5.79.

(E)-1-[2-(3-(2, 4-dimethoxyphenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.7)

Yield: 84%; yellow powder; m.p. 141 ^oC; IR (KBr, ν_{max} cm^{-1}): 1312.12 (SO_2, asymmetrical), 1153.89 (SO_2, symmetrical), 3225.52 (N−H), 1716.60 (C=O), 1655.91 (C=C), 2888.09 (C–H), 1593.56 (CONH), 1356.56 (C-N), 1528.06 (N-H bend) ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 3.85 (s, 9H, OCH_3), 7.41 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.66-7.98 (m, 3H, Ar-H), 7.69 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.85 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.98 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.01 (s, 1H, NH), 10.98 (s, 1H, NH); ESI-MS (*m/z*): 482 $[M]^+$; Anal. Calcd. for $C_{24}H_{23}N_3O_6S$, %: C, 62.49; H, 5.03; N, 5.83; Found, %: C, 62.23; H, 5.16; N, 5.78.

(E)-1-[2-(3-(3,4,5-trimethoxyphenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.8)

Yield: 88%; yellow powder; m.p. 115 ^oC; IR (KBr, ν_{max} cm^{-1}): 1280.09 (SO_2, asymmetrical), 1135.11 (SO_2, symmetrical), 3355.61, 3305.62 (N−H), 1595.57 (C=O), 1516.55 (C=C), 2976.70 (C–H), 1471.90 (CONH), 1307.86 (C-N), 1441.77 (N-H bend) ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.85 (s, 6H, OCH_3), 7.25 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.43-7.77 (m, 8H, Ar-H), 7.69 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.85 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.98 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 8.92 (s, 1H, NH), 10.41 (s, 1H, NH); ESI-MS (*m/z*): 512 $[M]^+$; Anal. Calcd.

For $C_{25}H_{25}N_3O_7S$, %: C, 61.16; H, 5.13; N, 5.49; Found, %: C, 61.22; H, 5.21; N, 5.51.

(E)-1-[2-(3-(2-hydroxyphenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.9)

Yield: 86%; yellow powder; m.p. 169 ^oC; IR (KBr, ν_{max} cm^{-1}): 1300.45 (SO_2, asymmetrical), 1153.94 (SO_2, symmetrical), 3225.64 (N−H), 1716.79 (C=O), 1655.81 (C=C), 1592.18 (C–H), 1449.91 (CONH), 1341.90 (C-N), 1528.01 (N-H bend) ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 7.37-7.93 (m, 7H, Ar-H), 7.47 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.70 (d, *J* = 15.4 Hz, 1H, HC=CH (H-α)), 7.81 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.88 (d, *J* = 15.4 Hz, 1H, HC=CH (H-β)), 10.12 (s, 1H, OH), 10.64 (s, 1H, NH); 11.98 (s, 1H, NH); ESI-MS (*m/z*):438 $[M]^+$; Anal. Calcd. for $C_{22}H_{21}N_3O_5S$, %: C, 63.29; H, 4.62; N, 6.42; Found, %: C, 63.33; H, 4.71; N, 6.55.

(E)-1-[2-(3-(3-hydroxyphenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.10)

Yield: 82%; yellow powder; m.p. 177 ^oC; IR (KBr, ν_{max} cm^{-1}): 1300.33 (SO_2, asymmetrical), 1153.95 (SO_2, symmetrical), 3226.13 (N−H), 1716.91 (C=O), 1655.97 (C=C), 1592.50 (C–H), 1449.90 (CONH), 1341.79 (C-N), 1528.90 (N-H bend) ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 7.22-7.63 (m, 7H, Ar-H), 7.42 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.45 (s, 1H, OH), 7.69 (d, *J* = 15.4 Hz, 1H, HC=CH (H-α)), 7.81 (d, *J* = 15.4 Hz, 1H, HC=CH (H-β)), 7.83 (d, *J* = 8.1 Hz, 2H, Ar-H), 10.87 (s, 1H, NH), 12.12 (s, 1H, NH); ESI-MS (*m/z*): 438 $[M]^+$; Anal. Calcd. for $C_{22}H_{19}N_3O_5S$, %: C, 63.29; H, 4.62; N, 6.42; Found, %: C, 63.31; H, 4.77; N, 6.51.

(E)-1-[2-(3-(4-hydroxyphenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.11)

Yield: 89%; yellow powder; m.p.188 ^oC; IR (KBr, ν_{max} cm^{-1}): 1304.42 (SO_2, asymmetrical), 1174.98 (SO_2, symmetrical), 3415.26, 3350.19 (N−H), 1616.27 (C=O), 1583.45 (C=C), 3057.17 (C–H), 1555.13 (CONH), 1337.89 (C-N), 1517.19 (N-H bend), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 7.43 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.66 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.67-8.12 (m, 7H, Ar-H), 7.86 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 7.87 (d, *J* = 8.1 Hz, 2H, Ar-H), 9.43 (s, 1H, OH), 9.45 (s, 1H, NH), 11.93 (s, 1H, NH); ESI-MS (*m/z*): 438 $[M]^+$; Anal. Calcd. for $C_{22}H_{19}N_3O_5S$, %: C, 63.29; H, 4.62; N, 6.42; Found, %: C, 63.32; H, 4.72; N, 6.55.

(E)-1-[2-(3-(3-ethoxy-4-hydroxyphenyl)acryloyl)-3-pyridinyl]-3-tosylurea (II.12)

Yield: 89%; yellow powder; m.p. 199 ^oC; IR (KBr, ν_{max} cm^{-1}): 1299.39 (SO_2, asymmetrical), 1090.78 (SO_2, symmetrical), 3381.27, 3346.19 (N−H), 1713.53 (C=O), 1664.97 (C=C), 3092.17 (C–H), 1595.27 (CONH), 1423.52 (C-N), 1536.30 (N-H bend), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 6.54 (s, 2H, CH_2), 6.82 (s, 3H, CH_3), 6.97-7.34 (m, 6H, Ar-H), 7.42 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.69 (d, *J* = 15.4 Hz, 1H, HC=CH (H-α)), 7.82 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.94 (d, *J* = 15.4 Hz, 1H, HC=CH (H-β)), 8.78 (s, 1H, OH), 10.45 (s, 1H, NH), 11.66 (s, 1H, NH); ESI-MS (*m/z*): 482 $[M]^+$; Anal. Calcd. for $C_{24}H_{23}N_3O_6S$, %: C, 62.49; H, 5.03; N, 5.83; Found, %: C, 62.58; H, 5.12; N, 5.89.

(E)-1-[2-(3-(3-methoxy-4-hydroxyphenyl)acryloyl)-3-pyridinyl]-3-tosylurea (II.13)

Yield: 93%; yellow powder; m.p. 211 ^oC; IR (KBr, ν_{max} cm^{-1}): 1313.66 (SO_2, asymmetrical), 1157.43 (SO_2, symmetrical), 3367.15, 3304.61 (N−H), 1726.95 (C=O), 1659.14 (C=C), 3058.13 (C–H), 1592.42 (CONH), 1345.87 (C-N), 1532.41 (N-H bend), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 6.85-7.45 (m, 6H, Ar-H), 7.42 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.87 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.68 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.96 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 8.43 (s, 1H, OH), 9.28 (s, 1H, NH), 10.87 (s, 1H, NH); ESI-MS (*m/z*): 468 $[M]^+$; Anal. Calcd. for $C_{23}H_{21}N_3O_6S$, %: C, 61.79; H, 4.75; N, 6.00; Found, %: C, 61.65; H, 4.66; N, 6.11.

(E)-1-[2-(3-(2-nitrophenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.14)

Yield: 86%; yellow powder; m.p. 128 ^oC; IR (KBr, ν_{max} cm^{-1}): 1304.99 (SO_2, asymmetrical), 1158.35 (SO_2, symmetrical), 3471.63, 3242.44 (N−H), 1708.60 (C=O), 1650.44 (C=C), 3092.42 (C–H), 1586.04 (CONH), 1349.69 (C-N), 1528.22 (N-H bend), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 6.95-7.18 (m, 7H, Ar-H), 7.41 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.69 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.87 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.95 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.22 (s, 1H, NH), 10.55 (s, 1H, NH); ESI-MS (*m/z*): 467 $[M]^+$; Anal. Calcd. for $C_{22}H_{18}N_4O_6S$, %: C, 59.35; H, 4.11; N, 9.03; Found, %: C, 59.32; H, 4.16; N, 9.21.

(E)-1-[2-(3-(3-nitrophenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.15)

Yield: 89%; yellow powder; m.p. 103 ^oC; IR (KBr, ν_{max} cm^{-1}): 1315.75 (SO_2, asymmetrical), 1161.71 (SO_2, symmetrical), 3413.71, 3263.98 (N−H), 1689.86 (C=O), 1625.16 (C=C), 3063.64 (C–H), 1585.44 (CONH), 1342.59 (C-N), 1521.96 (N-H bend); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 6.95-7.41 (m, 7H, Ar-H), 7.43 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.67 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.78 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.91 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 10.97 (s, 1H, NH), 11.94 (s, 1H, NH); ESI-MS (*m/z*): 467 $[M]^+$; Anal. Calcd. for $C_{22}H_{18}N_4O_6S$, %: C, 59.35; H, 4.11; N, 9.03; Found, %: C, 59.32; H, 4.23; N, 9.21.

(E)-1-[2-(3-(5-hydroxy-2-nitrophenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.16)

Yield: 85%; yellow powder; m.p. 290 ^oC; IR (KBr, ν_{max} cm^{-1}): 1306.40(SO_2, asymmetrical), 1156.38 (SO_2, symmetrical), 3383.17, 3290.68 (N−H), 1649.52 (C=O), 1614.05 (C=C), 3068.77 (C–H), 1581.60 (CONH), 1346.50 (C-N), 1547.63 (N-H bend); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 6.86-7.23 (m, 6H, Ar-H), 7.42 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.70 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.83 (d, *J* = 8.1 Hz,

2H, Ar-H), 7.88 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 8.42 (s, 1H, OH), 10.41 (s, 1H, NH), 11.72 (s, 1H, NH); ESI-MS (*m/z*): 483 $[M]^+$; Anal. Calcd. for $C_{22}H_{18}N_4O_7S$, %: C, 57.37; H, 3.98; N, 8.73; Found, %: C, 57.44; H, 3.78; N, 8.24.

(E)-1-[2-(3-(3-fluorophenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.17)

Yield: 84%; yellow powder; m.p. 310 °C; IR (KBr, ν_{max} cm^{-1}): 1294.93 (SO_2, asymmetrical), 1160.30(SO_2, symmetrical), 3241.17 (N−H), 1704.30 (C=O), 1647.48 (C=C), 3029.76 (C–H), 1591.30 (CONH), 1344.51 (C-N), 1522.50 (N-H bend) ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 7.18-7.97 (m, 8H, Ar-H), 7.41 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.66 (d, *J* = 15.4 Hz, 1H, HC=CH (H-α)), 7.88 (d, *J* = 8.1 Hz, 2H, Ar-H), 8.03 (d, *J* = 15.4 Hz, 1H, HC=CH (H-β)), 10.03 (s, 1H, NH), 11.16 (s, 1H, NH); ESI-MS (*m/z*): 440 $[M]^+$; Anal. Calcd. for $C_{22}H_{18}FN_3O_4S$, %: C, 63.00; H, 4.37; N, 6.39; Found, %: C, 63.12; H, 4.44; N, 6.43.

(E)-1-[2-(3-(4-fluorophenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.18)

Yield: 87%; yellow powder; m.p. 266 °C; IR (KBr, ν_{max} cm^{-1}): 1306.01 (SO_2, asymmetrical), 1156.37 (SO_2, symmetrical), 3383.19, 3289.69 (N−H), 1649.66 (C=O), 1615.33 (C=C), 3068.87 (C–H), 1581.40 (CONH), 1346.38 (C-N), 1512.29 (N-H bend); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 7.05-7.68 (m, 8H, Ar-H), 7.69 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.79 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.42 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.99 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.94 (s, 1H, NH), 11.01 (s, 1H, NH); ESI-MS (*m/z*): 440 $[M]^+$; Anal. Calcd. for $C_{22}H_{18}FN_3O_4S$, %: C, 63.00; H, 4.37; N, 6.39; Found, %: C, 63.12; H, 4.24; N, 6.32.

(E)-1-[2-(3-(2-chlorophenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.19)

Yield: 88%; yellow powder; m.p. 169 °C; IR (KBr, ν_{max} cm^{-1}): 1300.39 (SO_2, asymmetrical), 1153.34 (SO_2, symmetrical), 3225.84 (N−H), 1716.47 (C=O), 1695.95 (C=C), 3071.70 (C–H), 1684.27 (CONH), 1340.88 (C-N),1558.02 (N-H bend) ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 6.66-7.15 (m, 7H, Ar-H), 7.41 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.66 (d, *J* = 15.4 Hz, 1H, HC=CH (H-α)), 7.83 (d, *J* = 8.1 Hz, 2H, Ar-H), 8.05 (d, *J* = 15.4 Hz, 1H, HC=CH (H-β)), 10.89 (s, 1H, NH), 12.13 (s, 1H, NH); ESI-MS (*m/z*): 456 $[M]^+$; Anal. Calcd. For $C_{22}H_{18}ClN_3O_4S$, %: C, 60.72; H, 4.21; N, 6.16; Found, %: C, 60.65; H, 4.32; N, 6.14.

(E)-1-[2-(3-(4-chlorophenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.20)

Yield: 92%; yellow powder; m.p. 149 °C; IR (KBr, ν_{max} cm^{-1}):1270.32 (SO_2, asymmetrical), 1133.11 (SO_2, symmetrical), 3450.92, 3340.69 (N−H), 1650.02 (C=O), 1626.16 (C=C), 3049.92 (C–H), 1588.83 (CONH), 1341.23 (C-N), 1566.62 (N-H bend) ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 7.38 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.45-7.63 (m, 7H, Ar-H), 7.67 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.88 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.90 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.73 (s, 1H, NH), 11.21 (s, 1H, NH);ESI-MS (*m/z*): 456 $[M]^+$; Anal. Calcd. for $C_{22}H_{18}ClN_3O_4S$, %: C, 60.72; H, 4.21; N, 6.16; Found, %: C, 60.65; H, 4.37; N, 6.15.

(E)-1-[2-(3-(2,4-dichlorophenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.21)

Yield: 85%; yellow powder; m.p. 248 °C; IR (KBr, ν_{max} cm^{-1}): 1270.15 (SO_2, asymmetrical), 1135.27 (SO_2, symmetrical), 3454.74, 3345.63 (N−H), 1708.61 (C=O), 1633.30 (C=C), 3069.05 (C–H), 1617.33 (CONH), 1359.42 (C-N), 1584.03 (N-H bend); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 6.66-7.35 (m, 6H, Ar-H), 7.44 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.66 (d, *J* = 15.4 Hz, 1H, HC=CH (H-α)), 7.74 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.88 (d, *J* = 15.4 Hz, 1H, HC=CH (H-β)), 9.68 (s, 1H, NH), 10.91 (s, 1H, NH); ESI-MS (*m/z*): 491 $[M]^+$; Anal. Calcd. for $C_{22}H_{17}Cl_2N_3O_4S$, %: C, 56.45; H, 3.71; N, 5.72; Found, %: C, 56.53; H, 3.82; N, 5.86.

(E)-1-[2-(3-(3-bromophenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.22)

Yield: 84%; yellow powder; m.p. 154 °C; IR (KBr, ν_{max} cm^{-1}): 1306.19 (SO_2, asymmetrical), 1168.16 (SO_2, symmetrical), 3445.90, 3349.33 (N−H), 1642.93 (C=O), 1596.01 (C=C), 3068.33 (C–H), 1511.44 (CONH), 1334.62 (C-N), 1447.40 (N-H bend); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 7.35-7.68 (m, 7H, Ar-H), 7.41 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.69 (d, *J* = 15.4 Hz, 1H, HC=CH (H-α)), 7.78 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.98 (d, *J* = 15.4 Hz, 1H, HC=CH (H-β)), 9.12 (s, 1H, NH), 8.99 (s, 1H, NH); ESI-MS (*m/z*): 501 $[M]^+$; Anal. Calcd. for $C_{22}H_{18}BrN_3O_4S$, %: C, 55.32; H, 3.83; N, 5.61; Found, %: C, 55.28; H, 3.82; N, 5.55.

(E)-1-[2-(3-(4-allyloxyphenyl) acryloyl)-3-pyridinyl]-3-tosylurea (II.23)

Yield: 85%; yellow powder; m.p. 214 °C; IR (KBr, ν_{max} cm^{-1}): 1281.45 (SO_2, asymmetrical), 1127.75 (SO_2, symmetrical), 3328.09, 3227.67 (N−H), 1632.86 (C=O), 1588.71 (C=C), 3058.56 (C–H), 1502.90 (CONH), 1326.78 (C-N), 1458.19 (N-H bend); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 4.49 (s, 2H, CH_2),5.33 (s, 2H, CH_2), 5.51 (s, 1H, CH), 7.42 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.67-7.91 (m, 7H, Ar-H), 7.83 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.87 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 8.04 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 8.98 (s, 1H, NH), 9.96 (s, 1H, NH); ESI-MS (*m/z*): 478 $[M]^+$; Anal. Calcd. for $C_{25}H_{23}N_3O_5S$, %: C, 65.53; H, 5.08; N, 5.88; Found, %: C, 65.34; H, 5.90; N, 5.75.

(E)-1-[2-(3-(Phenylethene-yl) acryloyl)-3-pyridinyl]-3-tosylurea (II.24)

Yield: 94%; yellow powder; m.p. 254 °C; IR (KBr, ν_{max} cm^{-1}): 1301.84 (SO_2, asymmetrical), 1141.44(SO_2, symmetrical), 3443.47, 3297.97 (N−H), 1630.35 (C=O), 1573.17 (C=C), 3060.47 (C–H), 1509.31 (CONH), 1354.54 (C-N), 1447.23 (N-H bend); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 7.33-7.12 (m, 10H, Ar-H), 7.42 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.68 (d, *J* = 15.4 Hz, 1H, HC=CH (H-α)), 7.78 (d, *J* = 8.1 Hz,

2H, Ar-H), 7.92 (d, *J* = 15.4 Hz, 1H, HC=CH (H-β)), 10.97 (s, 1H, NH), 11.99 (s, 1H, NH); ESI-MS (*m/z*): 448 $[M]^+$; Anal. Calcd. For $C_{24}H_{21}N_3O_4S$, %: C, 67.25; H, 4.97; N, 6.27; Found, %: C, 67.18; H, 4.12; N, 6.23.

(E)-1-[2-(3-(pyrrole-2-yl) acryloyl)-3-pyridinyl]-3-tosylurea (II.25)

Yield: 89%; yellow powder; m.p. 129 °C; IR (KBr, ν_{max} cm^{-1}): 1300.01 (SO_2, asymmetrical), 1134.33 (SO_2, symmetrical), 3438.74, 3312.27 (N−H), 1631.65 (C=O), 1600.39 (C=C), 3037.82 (C–H), 1520.59 (CONH), 1347.13 (C-N), 1481.64 (N-H bend); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 7.18-7.23 (m, 6H, Ar-H), 7.42 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.64 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.79 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.87 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 9.11 (s, 1H, NH), 10.89 (s, 1H, NH), 12.21 (s, 1H, NH); ESI-MS (*m/z*): 411 $[M]^+$; Anal. Calcd. for $C_{20}H_{20}N_4O_4S$, %: C, 61.60; H, 4.68; N, 10.26; Found, %: C, 61.27; H, 4.29; N, 10.42.

(E)-1-[2-(3-(pyridine-3-yl) acryloyl)-3-pyridinyl]-3-tosylurea (II.26)

Yield: 86%; yellow powder; m.p. 164 °C; IR (KBr, ν_{max} cm^{-1}): 1303.04 (SO_2, asymmetrical), 1146.74 (SO_2, symmetrical), 3423.71, 3218.12 (N−H), 1686.78 (C=O), 1650.79 (C=C), 3016.71 (C–H), 1593.77 (CONH), 1352.78 (C-N), 1520.60 (N-H bend); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 6.97-7.54 (m, 7H, Ar-H), 7.41 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.68 (d, *J* = 15.4 Hz, 1H, HC=CH (H-α)), 7.88 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.93 (d, *J* = 15.4 Hz, 1H, HC=CH (H-β)), 10.45 (s, 1H, NH), 11.99 (s, 1H, NH); ESI-MS (*m/z*): 423 $[M]^+$; Anal. Calcd. for $C_{21}H_{20}N_4O_4S$, %: C, 62.69; H, 4.54; N, 9.97; Found, %: C, 62.69; H, 4.62; N, 9.78.

(E)-1-[2-(3-(pyridine-4-yl) acryloyl)-3-pyridinyl]-3-tosylurea (II.27)

Yield: 89%; yellow powder; m.p. 152 °C; IR (KBr, ν_{max} cm^{-1}): 1296.18 (SO_2, asymmetrical), 1156.82 (SO_2, symmetrical), 3388.52, 3277.16 (N−H), 1649.42 (C=O), 1620.73 (C=C), 2887.24 (C–H), 1586.18 (CONH), 13463.10 (C-N), 1498.36 (N-H bend); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 7.42 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.53-7.81 (m, 7H, Ar-H), 7.66 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.79 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.89 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 10.42 (s, 1H, NH), 11.64 (s, 1H, NH); ESI-MS (*m/z*): 423 $[M]^+$; Anal. Calcd. for $C_{21}H_{20}N_4O_4S$, %: C, 62.69; H, 4.54; N, 9.97; Found, %: C, 62.71; H, 4.66; N, 9.88.

(E)-1-[2-(3-(Anthracen-9-yl) acryloyl)-3-pyridinyl]-3-tosylurea (II.28)

Yield: 93%; yellow powder; m.p. 192 °C; IR (KBr, ν_{max} cm^{-1}): 1319.24 (SO_2, asymmetrical), 1157.40 (SO_2, symmetrical), 3298.78, 3242.28 (N−H), 1694.09(C=O), 1600.38 (C=C), 2887.04 (C–H), 1537.34 (CONH), 1343.27 (C-N), 1452.65 (N-H bend); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.30 (s, 3H, CH_3), 7.31-7.54 (m, 12H, Ar-H), 7.42 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.73 (d, *J* = 15.2 Hz, 1H, HC=CH (H-α)), 7.81 (d, *J* = 8.1 Hz, 2H, Ar-H), 8.11 (d, *J* = 15.2 Hz, 1H, HC=CH (H-β)), 10.78 (s, 1H, NH), 12.11 (s, 1H, NH); ESI-MS (*m/z*): 522 $[M]^+$; Anal. Calcd. For $C_{30}H_{23}N_3O_4S$, %: C, 71.52; H, 4.65; N, 5.38; Found, %: C, 71.48; H, 4.53; N, 5.25.

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