# SYNTHESIS AND BIOLOGIC PROPERTIES OF SOME1-(ALCHYL) PHENYL-3-(4-(3-(PYRIDIN-2-IL)ACRYLOYL)PHENYLTHIOUREA

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**Abstract**: This paper describe the synthesis of some 1-(alchyl)aril-3-(4-(3-pyridin-2-il) acryloyl)phenylthiourea obtained by condensation of 2-pyridincarboxaldehide with some derivatives of 4-acetylphenilthioureas in basic medium or by addition of aliphatic and aromatic amines to the correspondingisothiocyanatopropenones. 12 new compounds were obtained and their biological properties were analysed. The substituted thioureas by pyridine radicals, morpholine and phenol show a maximum bacteriostatic activity for Gram positive microorganisms like: *Staphylococcus Aureus* and *Enterococcus Faecalis* at the minimum inhibitory concentration 9.37-37.5 μM. Antifungal activity for *Candida Albicans*, *Aspergillus Niger*, *AspergillusFumigatus, Penicillium* is weak, in minimum inhibitory concentration 600->600 μM. The leukemia activity like inhibitor (HL-60), is 84-96.9% at the concentration $10^{-5}$mol/l and 15-20% and at the concentrations $10^{-6}$, $10^{-7}$mol/l.

**Keywords:** chalcones, isothiocyanatopropenones, thioureas, antibacterial activity, antifungal activity, antiproliferative activity

## Introduction

Some chalcones, arylheterilpropenone and their derivatives posses divers biological properties: inflammatory [1, 2], antioxidative [3], antituberculosis [4], anti malaria [5], antifungal and antibacterial [6, 7], anticancer [8-12] etc. The testation of chalcones [8] like proliferates inhibitors of cancer cells showed that their activity depend by the substituent (OH, $OCH_3$) position on the benzene nuclei. Some chalcones [13] with thioamids groups exhibit higher anticancer action then in those without sulphur. For chalcones with thioureea groups was detected a pronounced antinociceptive activity [14]. The chalcones [15] (with OH, $OCH_3$, $OCH_2$=$CH_2$ groups) extracted from Chinese Licorice roots have a strong antileishmanial activity. Robinson et all. [11], showed that the enon fragment of the chalconesincrease the biological activity.

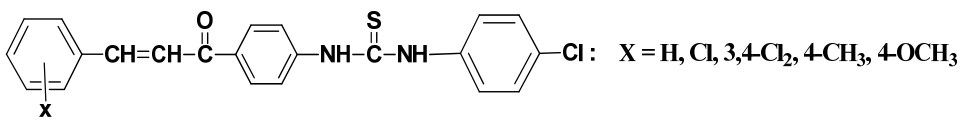
Some derivatives, obtained from chalcones through chemical transformations are also biologically active compounds. The modification of the chalcones on the carbonyl group with some hydrazine derivatives, followed by cyclisation [16], leads to 1,3,5-substituted pyrazolines with anticonvulsant and antidepressant properties. Were identified bacterial species which can modify and cyclisedchalcones in biologically active flavonoids [17].

In the literary sources mentioned above, the chalcones are obtained through the condensation of the aromatic and heterocyclic aldehides with acetyl arenes or by modifying the functional groups [18]. 1,3-Pyridylphenylpropenones with thiourea groups are less studies and became our object of study.

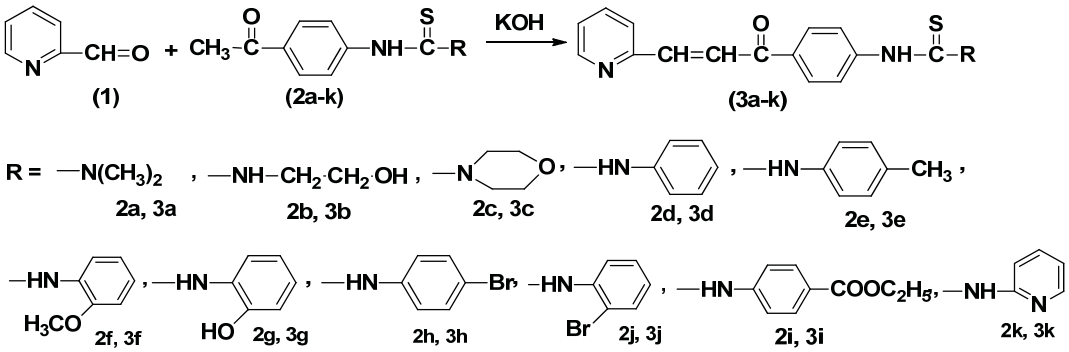
## Results and discussion

### Chemistry

The first chalcones [14] with thiourea groups were obtained by Claisen-Schmidt condensation of a 1-(4-acetylphenyl)-3-(4-clorophenyl)thiourea with different aromatic aldehides:



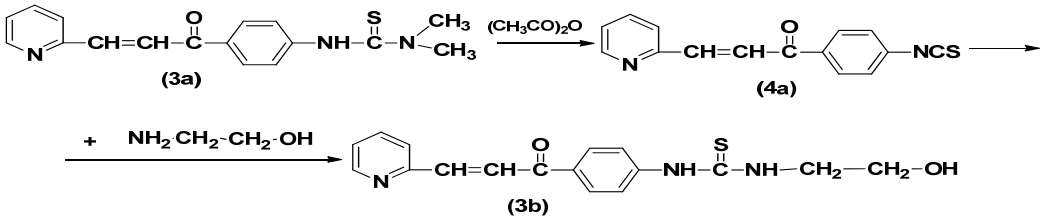

We obtained 3-(4-(3-pyridin-2-il)acryloyl)phenyl-1-(alchil)arilthiourea with similar structure as illustrated below:




4-Acetylphenylthiourea 2a was obtained [19] by heating 1-(4-aminophenyl)ethanonewith tetramethyltiuram disulphide (DTMT) in dimethylformamide (82%, m.p.= 175-176°C).4-Acetylphenylthioureas**2b-k** were synthesised by addition of the corresponding amines to the4-isothiocyanatoacetophenone [20].

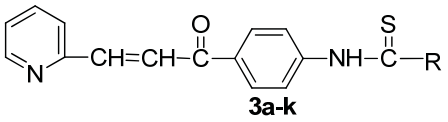
The condensation of the thioureas **2a-k** with 2-pyridincaboxaldehide**1** in alkaline catalysis lead to 1,3-arilpyridilpropenones**3a-k** with thioureas groups. Silofol thin layer chromatography showed that the reactions take place easy, with good yields, but with small quantities of secondary products which can be isolated by recristallisation from ethanol.

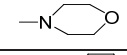
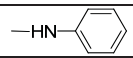
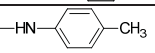
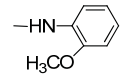
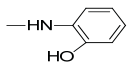
Alternative method of synthesis of thiourea **3b** was investigated following the transformations:

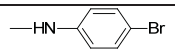
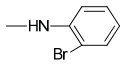
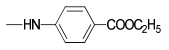
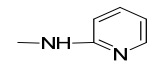



By heating the thiourea **3a**withaceticanhydride is obtained the 1-(4-isothiocyanatophenyl)-3-(pyridin-2-il)prop-2-en-1-one**4a** with 53% of yield. The addition of the monoethanolamine to the isothiocyanate **4a**, lead to thiourea **3b** with 92% of yield. The synthesis of thioureas **3b-k** in this way is less convenient because of low yield (53%) of the isothiocyanate **4a**. The solvents and reagents were purified in the usual manners where necessary. The structure of the compounds**3a-k** and **4a** were confirmed by the elemental and spectral analysis ($^{13}C$, $^{1}H$-NMR).The NMR ($^{13}C$, $^{1}H$-NMR) spectra were recorded on a Bruker DRX-400spectrometer at room temperature. All chemical shifts ($^{1}H$, $^{13}C$) are given in ppm versus $SiMe_4$ using DMSO – $d_6$ as solvent.

*Table 1*

**The compounds with the formula:** 


| Nr. | R | Formula | Found/Calculated, % | | | M. P., $^0C$ | Yield, % |
|---|---|---|---|---|---|---|---|
| | | | C | H | N | | |
| 3a | $-N(CH_3)_2$ | $C_{17}H_{17}N_3OS$ | 65.03/65.57 | 5.98/5.50 | 14.00/13.49 | 180-182 | 89 |
| 3b | $-NH-CH_2-CH_2OH$ | $C_{17}H_{17}N_3O_2S$ | 62.31/62.36 | 5.20/5.23 | 12.80/12.83 | 124-125 | 80 |
| 3c |  | $C_{19}H_{19}N_3O_2S$ | 64.92/64.57 | 6.35/5.42 | 11.72/11.89 | 145-146 | 89 |
| 3d |  | $C_{21}H_{17}N_3OS$ | 70.52/70.17 | 4.81/4.77 | 11.64/11.69 | 155-156 | 75 |
| 3e |  | $C_{22}H_{19}N_3OS$ | 70.93/70.75 | 5.29/5.13 | 11.38/11.25 | 134-136 | 82 |
| 3f |  | $C_{22}H_{19}N_3O_2S$ | 67.90/67.84 | 4.89/4.92 | 10.81/10.79 | 142-143 | 79 |
| 3g |  | $C_{21}H_{17}N_3O_3S$ | 67.26/67.18 | 4.50/4.56 | 11.38/11.19 | 163-165 | 68 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 3h |  | $C_{21}H_{16}BrN_3O_2S$ | 57.19/57.54 | 4.84/3.68 | 9.69/9.59 | 149-150 | 82 |
| 3j |  | $C_{21}H_{16}BrN_3O_2S$ | 57.22/57.54 | 4.90/3.68 | 9.64/9.59 | 159-162 | 79 |
| 3i |  | $C_{24}H_{21}N_3O_3S$ | 66.00/66.80 | 5.18/4.91 | 9.34/9.74 | 123-125 | 78 |
| 3k |  | $C_{20}H_{16}N_4OS$ | 65.49/66.65 | 5.14/4.47 | 15.75/15.54 | 197-199 | 87 |

Elemetal analyses (C, H, N) were performed on a Elemental Analyza Vario EL (III).

The melting points were determined with a Melting point meter A. KRUSS OPTRONIC Germania KSP-1N 90-26V/Al.

**Antibacterial activity**

The antibacterial activity (bacteriostatic and bactericidal) of the **3a-k** substances was investigated for the microorganisms: *Staphylococcus Aureus*, *Enterococcus Faecalis*, *Esscherichia coli*, *Proteus Vulgaris*, *Pseudomonas Aeruginosa* by serial dilution method in liquid nutrient medium (meat peptone broth 2%, pH = 7,0).

For sowing were used cultures of indicated microorganisms, grown on agar during 18 hours and washed with isotonic solution of sodium chloride. Insemination dose is 500 thousand copies for 1 mL of nutrient medium. The tubes were shaken and thermostated at 37°C during 24 hours. As control were used nutrients media inoculated with the same strains but without investigated substances. Evaluation of bacteriostatic activity (CMI) was carried out visually, as lack of growths of microorganisms in the broth. Bacterial activity (CMB) was determined based on the lack of growth of microorganisms after repeated seeding on peptone agar with subsequent thermostating for 24, 48 hours.

The obtained results are presented in Table 2.

*Table 2*

**Antibacterial activity of compounds*3a-k***

| Nr. | **Microorganisms. Antibacterial activity for the – Tests (mcg/ml)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Staphylococcus Aureus* | | *Enterococcus Faecalis* | | *Escherichia Coli* | | *Proteus Vulgaris* | | *Pseudomonas Aeruginosa* | |
| | *CMI | **CMB | CMI | CMB | CMI | CMB | CMI | CMB | CMI | CMB |
| 3a | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 |
| 3b | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 |
| 3c | 37,5 | >300 | 37,5 | >300 | >300 | >300 | >300 | >300 | >300 | >300 |
| 3d | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 |
| 3e | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 |
| 3f | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 |
| 3g | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 |
| 3h | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 |
| 3j | 9,37 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 |
| 3i | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 |
| 3k | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 | >300 |
| Furaciuyline | 18,7 | 37,5 | 37,5 | 75 | 18,7 | 37,5 | 150 | >300 | >300 | >300 |

*MIC – minimum inhibitory concentration. **MBC – minimum bactericide concentration.

The investigation results show that the substance **3c** posses bacteriostatic activity for Gram-positive microorganisms: Staphylococcus Aureus and Enterococcus Faecalis at concentration of 37.5 mcg/mL. The substance **3j** show bacteriostatic activity for S. Aureus (minimum inhibitory concentration is 9.37 μM) which prevail furaciline activity 2 times; minimum antibacterial concentration of this substance for Staphylococcus Aureus and for the other test bacterial cultures (Table 2) investigated is more than 300 μM.

Bacteriostatic and bactericidal action of substances **3a, 3b, 3d-f,3h,3i,3k** for all test bacterial cultures investigated is at concentrations above 300 μM.

**Antifungal activity**

Antifungal activity of compounds **3a-k** was investigated for fungi: *Candida Albicans, Aspergillus Niger, Aspergillus Fumigatus, Penicillium*. Initially, the substances were dissolved in dimethylformamide (concentration 10 mg/mL) and subsequent concentrations were obtained using serial dilution method in broth (broth Saburo). The inoculates were prepared from cultures of fungi. After mixing the inoculates with the solutions of investigated substances, the tubes were exposed in thermostat at 28°C during 14 days (Candida Albicans during 48 hours). Antifungal activity was determined by the absence of the fungal growth in a repeated sowing on Saburo agar with incubation during 7 days (Candida albicans during 48 hours).

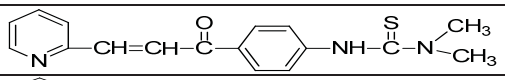
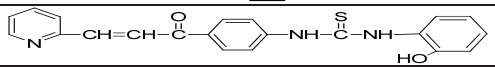
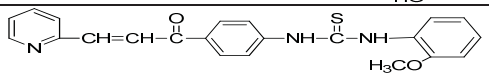
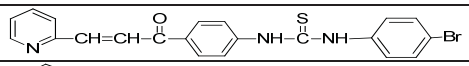
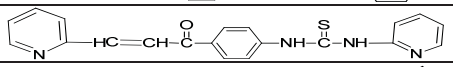
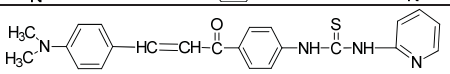
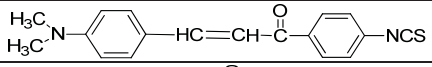
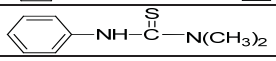
The investigation results show that the substances **3a-k** possess antifungal activity for Candida albicans, Aspergillus Niger, Aspergillus Fumigatus, Penicillium in minimum inhibitory concentration of 600 and…>600 μM.

**Antileukemia activity (HL-60)**

Cell culture. Human promyelocytic leukemia cells HL-60 (ATCC, Rockville, MD, USA) were routinely grown in suspension in 90% RPMI-1640 (Sigma, Saint Louis, USA) containing L- glutamine (2 nM), antibiotics (100 IU penicillin/mL, 100 mg streptomycin/mL) and supplemented with 10% (v/v) foetal bovine serum (FBS), in a 5% $CO_2$ humidified atmosphere at 37°C. Cells were currently maintained twice a week by diluting the cells in RPMI 1640 medium containing 10% FBS. Cellproliferation assay. The cell proliferation assay for compounds and ligands was performed using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl) 2-(4-sulfophenyl)-2H-tetrazolium (MTS) (Cell Titer 96 Aqueous, Promega, USA), which allowed us to measure the number of viable cells. In brief, triplicate cultures of 10,000 cells in a total of 100 mL medium in 96-well microtiter plates (Becton Dickinson and Company, Lincoln Park, NJ, USA) were incubated at 37°C, 5% $CO_2$. Compounds were dissolved in ethanol to prepare the stock solution of 1 J 1022 M. These compounds and doxorubicin (Novapharm, Toronto, Canada), as a positive control, were diluted at multiple concentrations (1 and 10 μM) with culture media, added to each well and incubated for 3 days. Following each treatment, MTS (20 μL) was added to each well and the mixture incubated for 4 hours. MTS is converted to water-soluble colored formazan by dehydrogenase enzymes present in metabolically active cells. Subsequently, the plates were read at 490 nm using a microplate reader (Molecular Devices, Sunnyvale, CA).

**Table 3**

**Antiproliferative activity of thioureas onhuman leukemia (HL-60) cells at two concentrations**

| Nr. | Compound | Inhibition of cell proliferation ( %) | | |
|---|---|---|---|---|
| | | Concentrates, mol/l | | |
| | | $10^{-5}$ | $10^{-6}$ | $10^{-7}$ |
| **3a** |  | 84.0 | 6.2 | 0 |
| **3g** |  | 92.6 | 22.8 | 15.7 |
| **3f** |  | 84.2 | 23.0 | 17.8 |
| **3h** |  | 92.6 | 19.8 | 18.7 |
| **3k** |  | 96.9 | 13.7 | 18.4 |
| **6a** |  | 24.0 | 23.8 | 10.8 |
| **7a** |  | 0 | 0 | 0 |
| **8a** |  | 0 | 0 | 0 |
| **Dox** | **Dox-** doxorubic | 100 | 100 | 100 |

[a]SEM <± 4% of a single experiment in triplicate, **Dox –** doxorubicin of a single experiment in triplicate,

***7a** and **8a**are known [22, 23]

If we look at the compounds **3a**, **3g**, **3f**, **3h**, **3k** like derivatives of thiourea, we observe that their anticancer activity depends strongly on structure and varies from 0...96.9% for the compound concentration $10^{-5}$mol/L and from 0...23.8% for concentrations $10^{-6}$, $10^{-7}$mol/L. The introduction of a 2 pyridincarbonil radical in the thiourea molecule (compound **3a**) increase suddenly the activity from 0 to 84%, which is also mentioned for the other inhibitors with the

enon structure [11]. Replacing methyl groups in thiourea **3a** with the rest of phenol compound**3g** increases activity, but is reduced by ~8% for thiourea **3f**, when the hydroxyl group is methylated. The compounds **3g** and **3h** have almost the same activity, which is maximal for thiourea **3k** (96.9%), which contain in his structure two pyridine residues. A. Gulea et all. [21] explain the activity of anticancer inhibitors by the formation of hydrogen bonds with ADN cancerous cells. Indeed this type of interaction can be maximum for thiourea 3k with two pyridine nuclei. For compound 3k, when the structural fragment of 2-pyridil acryloyl is replaced by 4-dimethylaminophenyl-(thiourea**6a**), the activity decrease to 24%. In the case of compounds **7a** and **8a** with more pronounced hydrophobic character when the hydrogen bonds with the substrate are weaker, the activity is zero.

**Conclusion**

1-(alkyl)aryl-3-(4-(3-pyridin-2-yl)phenylthioureas **3a-k** are obtained with better efficiency by condensation of 4-acetilfenilthioureas derivatives with 2-pyridincarboxaldehide in the basic medium. The synthesis of this thioureas by the addition of aliphatic or aromatic amines to 1-(4-isothiocyanatophenyl)-3-(pyridin-2-il)prop-2-en-1-one is inconvenient; the respective isothiocyanate with rest of pyridine is unstable and is isolated with a relatively low yield.

The biological research has shown:

- The thioureas with the rest of morpholine **3c** and o-bromfenil **3j**possess bacteriostatic activity more pronounced for microorganisms Staphylococcus Aureus and Enterococcus Faecalis.

- The antifungal activity of compounds **3a-k** is weak.

- The antileukemia activity (HL-60) depends on the compounds structure; inhibition ranging from 24...96.9% for concentrations $10^{-5}$ mol/l. The thiourea,**3k** with two pyridine nuclei have maximal activity.

**Experimental section**

**Synthesis of 1,1-dimethyl-3-(4-(3-(pyridin-2-il)-acryloyl)-phenyl)thiourea (3a).** To the solution of 3-(4-Acetylphenyl)-1,1-dimethylthiourea**2a** (2.22 g, 0.01 mol) and 6 mL of dimethylformamide was added under stirring potassium hydroxide (1 g, 0.02 mol) dissolved in 4 mL of ethanol. After, the 2-pyridincarboxialdehide (1.28 g,0.012mol) in 4 mL of ethanol was added dropwise and the temperature maintained at 5-10°C. The resulting mixture was keep at room temperature for 12 hours. The impurities was isolated by filtration and the resulting solution was neutralized until pH = 7-8 to afford 2.78 g (89%) of thiourea**3a**, m.p. = 180-182°C. $^{1}$H-NMR (DMSO-$d_6$), ppm: 3.30 (s, 6 H, N($CH_3$)$_2$), 7.43-8.19 (m, 10H, =CH, Ar-H), 9.36 (s, 1H, NH). $^{13}$C-NMR (DMSO-$d_6$), ppm: 187.82 (C=O), 181.39 (C=S), 144.47 (C-N), 144.73 (-**CH**=CH**)**, 126.97 (-CH=CH), 154.79, 136.82, 131.37, 131.11, 128.84, 40.44, 40.23.

**Synthesis of 1-(2-hidroxietil)-3-(4-(3-(piridin-2-il)acryloyl)phenyl)thiourea (3b)**

**a)** To the solution of 1-(4-acetylphenyl)-3-(2-hydroxyethyl)thiourea 0.64 g, (0.002 mol) dissolved in minimum quantity of DMF was added potassium hydroxide 0.27 g(0.0048 mol) dissolved in 4 mL of ethanol. After, a solution of 2-pyridincarboxialdehide0.2 g, (0.002 mol) in 2.5 mL of ethanol was added under vigorous stirring at 10-20°C. The resulting mixture was neutralized with hydrochloric acid until pH = 7 and cooled down to room temperature. The yellow crystals was isolated by filtration 0.52 g (80%), m.p. = 124-125°C.

**b)** The mixture of 1-(4-isothiocyanatophenyl)-3-(pyridin-2-il)prop-2-en-1-one **4a**0.53 g, (0.002 mol), monoethanolamine 0.12 g, (0.002 mol) and 2 mL of acetone was kept at room temperature for 30 minutes, after boiled for 5 minutes and then cooled down to room temperature. The resulting crystals were isolated by filtration,to obtain 0.60 g (92%) of thiourea**3b**,m.p. = 124-125°C. $^{1}$H-NMR (DMSO-$d_6$), ppm: 7.41-8.69 (m, 13H, =CH, Ar-H), 10.08 (s,1H, NH-$C_6H_4$), 10.00 (s, 1H, NH-$CH_2$), 3.6(m, 4H, N-$CH_2$-$CH_2$-O), 4.09 (s, 1H, OH). $^{13}$C- NMR (DMSO, $d_6$), ppm: 188.26 (C=O), 180.65 (C=S), 143.40 (-CH=CH), 126.67 (-CH=CH), 46.95 (-$CH_2$-$CH_2$-OH), 59.48 (-$CH_2$-$CH_2$-OH).

**The 3c-k thioureas were obtained in the similar way.**

**N-(4-(3-(Pyridin-2-yl)acryloyl)phenyl)morfoline-4-carbothioamide 3c.**$^{1}$H-NMR (DMSO-$d_6$), ppm: 7.42-8.70 (m, 10H, =CH, Ar-H), 9.72 (s, 1H, NH-$C_6H_4$), 3.66-3.93(m, 8H, N-($CH_2$-$CH_2$)$_2$O). $^{13}$C-NMR (DMSO, $d_6$), ppm: 188.42 (C=O), 181.72 (C=S), 142.88 (-CH=CH), 125.67 (-CH=CH), 146.47 (C-N), 66.26 (-O-$CH_2$), 49.36 (-N-$CH_2$), 153.39, 137.67, 132.70, 129.42, 125.30, 123.48.

**1-Phenyl-3(4-(3-(pyridin-2-yl)acryloyl)phenyl)thiourea 3d.** $^{1}$H-NMR (DMSO-$d_6$), ppm: 8.71-7.14 (m, 15H, =CH, Ar-H), 10.14 (s,1H, NH-$C_6H_4$), 10.09 (s, 1H, NH-$C_6H_5$). $^{13}$C-NMR (DMSO-$d_6$), ppm: 188.39 (C=O), 179.79 (C=S), 142.97 (-CH=CH), 125.67 (-CH=CH), 137.69 ($C_6H_5$-NH), 145.12 (C-N), 153.37, 150.48, 132.93, 129.84, 122.17, 124.16.

**1-(4-(3-(Pyridin-2-yl)acryloyl)phenyl)-3-(p-tolyl)thiourea 3e.**$^{1}$H-NMR (DMSO-$d_6$), ppm: 7.20-8.71 (m, 14H, =CH, Ar-H), 9..25 (s, 1H, 2NH-$C_6H_4$), 9.22 (s, 1H, NH-$C_6H_4$)3.62 (s, 3H, $CH_3$).$^{13}$C-NMR (DMSO-$d_6$), ppm: 188.37 (C=O), 179.62 (C=S), 142.90 (-CH=CH), 144.38 ($C_6H_5$-NH**),** 122.14, 127.3, 137.26, 131.05.

**1-(2-Methoxyphenyl)-3-(4-(3-(pyridin-2-yl)acryloyl)phenyl)thiourea 3f.** $^{1}$H-NMR (DMSO-$d_6$), ppm: 3.75 (s, 3H, $OCH_3$), 6.83-8.71 (m, 14H, =CH, Ar-H), 9.77 (s, 1H, NH-$C_6H_4$), 10.21 (s, 1H, NH-$C_6H_4$). $^{13}$C-NMR (DMSO, $d_6$), ppm: 188.38 (C=O), 180.68 (C=S), 142.85 (-CH=CH), 126.65 (-CH=CH), 153.31 (-$C_6H_4$-$OCH_3$), 144.38 (C-N), 59.93 (-O-$CH_3$), 153.31, 150.40, 145.15, 137.78, 130.90, 129.81, 125.33, 122.22, 121.75.

**1-(2-Hydroxyphenyl)-3-(4-(3-(pyridin-2-yl)acryloyl)phenyl)thiourea 3g.** $^{1}$H-NMR(DMSO-$d_6$), ppm: 8.71-6.56 (m, 13H, =CH, Ar-H), 10.17 (s,1H, NH-$C_6H_4$), 9.52 (s, 1H, NH-$C_6H_4$-OH). $^{13}$C-NMR (DMSO-$d_6$), ppm: 188.40 (C=O), 179.38 (C=S), 142.88 (-CH=CH), 153.35 (-$C_6H_4$-OH), 157.99 (C-N), 127.09 (-CH=CH), 145.11, 140.59, 137.74, 132.86, 125.75, 122.20, 114.39.

**1-(4-Bromophenyl)-3-(4-(3-(pyridin-2-yl)acryloyl)phenyl)thiourea 3h.** $^{1}$H-NMR (DMSO-$d_6$), ppm: 8.7-7.41 (m, 14H, -$C_6H_3$ and =CH), 10.32 (s,1H, NH-$C_6H_4$), 10.22 (s, 1H, NH-$C_6H_4$-Br). $^{13}$C-NMR (DMSO-$d_6$), ppm: 188.49 (C=O), 179.83 (C=S), 143.00 (-CH=CH), 126.07 (-CH=CH), 122.42 ($C_6H_4$-Br), 153.40, 149.37, 144.76, 131.80, 133.18, 129.83, 137.61, 137.27.

**1-(2-Bromophenyl)-3-(4-(3-(pyridin-2-yl)acryloyl)phenyl)thiourea 3j.** $^{1}$H-NMR (DMSO-$d_6$), ppm: 8.7-7.41 (m, 14H, -$C_6H_3$ and =CH), 10.32 (s,1H, NH-$C_6H_4$), 10.22 (s, 1H, NH-$C_6H_4$-Br). $^{13}$C-NMR (DMSO-$d_6$), ppm: 188.49 (C=O), 179.83 (C=S), 143.00 (-CH=CH), 126.07 (-CH=CH), 122.42 ($C_6H_4$-Br), 153.40, 149.37, 144.76, 131.80, 133.18, 129.83, 137.61, 137.27.

**Ethyl 4-(3-(4-(3-(pyridin-2-yl)acryloyl)phenyl)thioureido)benzoate 5i.** $^{1}$H-NMR (DMSO-$d_6$), ppm: 6.55-8.70 (m, 14H, =CH, Ar-H), 10.53 (s, 1H, NH-$C_6H_4$), 10.46 (s, 1H, NH-$C_6H_4$), 4.33-4.28(m, 2H, -$CH_2$-O), 1.34(m, 3H -$CH_3$). $^{13}$C-NMR (DMSO, $d_6$), ppm: 188.47 (C=O), 179.58 (C=S), 165.78 (C=O-O-$C_2H_5$), 144.30 (-CH=CH), 125.67 (-CH=CH), 144.61 (C-N), 60.99 (-O-$CH_2$), 14.68 (-$CH_3$), 153.38, 150.50, 137.66, 133.29, 130.24, 129.87, 125.30, 122.55.

**1-(Pyridin-2-yl)-3-(4-(3-(pyridin-2-yl)acryloyl)phenyl)thiourea 3k.** $^{1}$H-NMR (DMSO-$d_6$), ppm: 7.13-8.71 (m, 14H, =CH, Ar-H), 10.53 (s, 1H, **NH**-Py), 10.46 (s, 1H, NH-$C_6H_4$). $^{13}$C-NMR (DMSO, $d_6$), ppm: 188.59 (C=O), 178.39 (C=S), 143.27 (-CH=CH), 125.59 (-CH=CH), 143.85 (C-N), 153.84, 153.31, 150.51, 137.67, 134.21, 129.75, 125.39, 122.55.

**Synthesis of 1-(4-isothiocyanatophenyl)-3-(pyridine-2-yl)prop-2-en-1-one 4a.** The mixture of 1,1-dimethyl-3-(4-(3-(pyridin-2-il)-acryloyl)-phenyl)thiourea (0.6 g, 0.02 mol), acetic anhydride (0.2 g, 0.002 mol) and 7 mL ethyl acetate was stirred at 60-65°C during 3 hours. The end of the reaction was follow by the totally consumption of the thiourea**3a**. The mixture was stirred until the thiourea 3a was totally consumed. The resulting product was washed with $NaHCO_3$ solution and after dried with anhydrous $Na_2SO_4$. The organic layer was diluted with hexane (2:1) and chromatographed on Silica Gel (eluent hexane/benzene 1:1). The solvent was removed *in vacuo* to afford 0.28 g (53%) of isothiocyanatopropenone **4a**, m.p. = 124-126°C.Elemental and spectral analysis: Found, %: C, 67.75; H, 3.88; N,10.62. Calculated, %: C, 67.65; H, 3.78; N,10.52.$^{1}$H-NMR(DMSO-$d_6$), ppm: 7.37-8.70 (m, 10H, =CH, Py-H, Ar-H). $^{13}$C-NMR (DMSO-$d_6$), ppm: 189.34 (C=O), 181.39 (C=S), 143.96 (-CH=CH**)**, 126.89 (-CH=CH).

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