Ultrasonic-Promoted Three-Component Synthesis of Some Biologically Active 1,2,5,6-Tetrahydropyrimidines

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Multicomponent reactions and organic synthesis with ultrasonic activation have been used as key methods for the synthesis of tetrahydropyrimidine derivatives. The three-component condensation of 1,3-diarylprop-2-en-1-one with ammonia and aldehydes/acetone or N-substituted γ-pyridones under ultrasonic irradiation was developed as a rapid and efficient solution-phase method for the high-yielding preparation of 2-aryl-(hetaryl)-4,6-diaryl-1,2,5,6-tetrahydropyrimidines and 2,4-diaryl-1,5,9-triazaspiro[5.5]undec-1-enes. The described synthetic protocol provides rapid access to novel and diversely substituted tetrahydropyrimidines libraries. The simple, primary biological screening showed 98% of inhibitory activity against *Mycobacterium tuberculosis* for one of tetrahydropyrimidines synthesized.

Introduction

The importance of partially hydrogenated pyrimidine derivatives in medicinal chemistry is widely known. Compounds of this class show several types of physiological activity[1] and, moreover, are suitable for subsequent chemical modification, which allows the synthesis of large libraries of new heterocycles. Among them, few studies have been performed on 1,2,5,6-tetrahydropyrimidines because of a paucity of efficient synthetic routes. To date, only two practically acceptable synthetic approaches for these compounds have been described.[2,3]

The first is a two-step pathway consisting of the reaction of aromatic aldehydes and ammonia producing *N*,*N*′-bis-(arylmethylidene)arylmethanediamines, followed by treatment with ketones containing active hydrogen in the α-position.[2a] However, this method has serious disadvantages: (i) impossibility of introducing different substituents into positions 2 and 6 of the heterocycle and (ii) the second step being highly dependent on the nature of the ketone.

The second method is the treatment of α,β-unsaturated ketones, carbonyl compounds, and ammonia at room temperature. This method was first developed for the synthesis of alkyl-substituted 1,2,5,6-tetrahydropyrimidenes[2b] in aqueous media and then, in our previous work, was extended for the aryl derivatives.[3] This method enabled the independent variation of four substituents on the pyrimidine ring and synthesis of large libraries of target heterocycles. However, this route also possesses several weaknesses: (i) long reaction time of up to 48 h, (ii) the formation of many byproducts and a very low yield with poorly soluble starting materials, and (iii) some heterocyclic aldehydes (nicotinic, 2- and 3-thiophenic, 2-furanic, etc.) and γ-pyridones simply being unreactive. Thus, our efforts concentrated on the development of efficient protocols for the preparation of arrays of these chemotypes, driven by a desire to explore their inherent physiological properties.

The efficient high-throughput synthesis of organic compounds is one of the most important objectives in modern drug discovery. Organic reactions should be fast and facile, and the target products should be easily separated and purified in high yields. From this point of view, there is much interest in the implementation of new processes and new synthetic strategies. Nonclassical methods, microwave-assisted synthesis, ultrasonic irradiation, and supercritical fluids, find application as methods to achieve these goals.

It is known that controlled microwave irradiation has proven to be a powerful tool for both reaction optimization and for the efficient preparation of new target compounds related to drug discovery projects.[4] However, the existing protocols do not meet these criteria: the reaction of α,β-unsaturated ketones with carbonyl compounds and ammonia is carried out at room temperature and even a slight heating leads to resinification of the reaction mixture and dramatically decreases yields of the resulting products.

Ultrasonic activation, based on cavitation effects leading to mass transfer improvement, is widely used today to promote numerous organic reactions, like dehydration,[5a,b] hydrogenation,[5c−e] Wittig−Horner condensations,[5f,h] cross-coupling Suzuki and Heck reactions,[5i−k] heterocyclizations,[5l,m] and many others.[6] After several decades of study, ultrasonic radiation has shown a short reaction time, good yields, and mild reaction conditions.

Thus, the present article is devoted to the ultrasonic-assisted synthesis of 4,6-diaryl-1,2,5,6-tetrahydropyrimidines of type **23** and **24** by three-component condensation of 1,3-diarylprop-2-en-1-ones (chalcones) with ammonia and carbonyl compounds. Our interest in these target heterocycles is stimulated by their close structural relationship to mol-

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Table 1. Synthesis of 2,4,6-Trisubstituted 1,2,5,6-Tetrahydropyrimidines

building blocks							
unsaturated ketones **1**−**7**			carbonyl compounds **8**−**21**			tetrahydropyrimidines **22, 23**	
compound	R_1	R_2	compound	R_3	R_4	compound	yield
1	2-HOC_6-H_4	4-FC_6H_4	**8**	H	H	**23a**	80
2	C_6H_5	2-HOC_6-H_4	**9**	C_6H_5	H	**23b**	85 (70)[b]
3	2-HOC_6-H_4	β-C_5H_4N	**10**	4-ClC_6H_4	H	**23c**	85[a]
4	3.4-$OCH_2OC_6H_3$	2-OH-5-ClC_6H_3	**11**	4-Br-C_6H_4	H	**23d**	85[a] (73)[b]
5	4-$CH_3C_6H_4$	2-HOC_6-H_4	**12**	CH_3	CH_3	**23e**	80 (58)[b]
6	C_6H_5	2-HO-5-ClC_6H_3	**13**	β-C_4H_3S	H	**23f**	85[a]
7	2-HOC_6-H_4	2-HOC_6-H_4	**14**	α-C_4H_3S	H	**23g**	85[a]
2	C_6H_5	2-HOC_6-H_4	**14**	α-C_4H_3S	H	**23h**	80
2	C_6H_5	2-HOC_6-H_4	**15**	α-(3-$CH_3C_4H_3S$)	H	**23i**	75
7	2-HOC_6-H_4	2-HOC_6-H_4	**16**	α-C_5H_4N	H	**23j**	90
2	C_6H_5	2-HOC_6-H_4	**17**	$C_6H_5CH_2$		**24a**	85
7	2-HOC_6-H_4	2-HOC_6-H_4	**18**	$CH(CH_3)_2$		**24b**	85
7	2-HOC_6-H_4	2-HOC_6-H_4	**19**	CH_3		**24c**	90
7	2-HOC_6-H_4	2-HOC_6-H_4	**20**	C_2H_5		**24d**	75
7	2-HOC_6-H_4	2-HOC_6-H_4	**21**	$COOC_2H_5$		**24e**	95
7	2-HOC_6-H_4	2-HOC_6-H_4	**22**	CH_3CO		**24f**	90
7	2-HOC_6-H_4	2-HOC_6-H_4	**17**	$C_6H_5CH_2$		**24g**	95

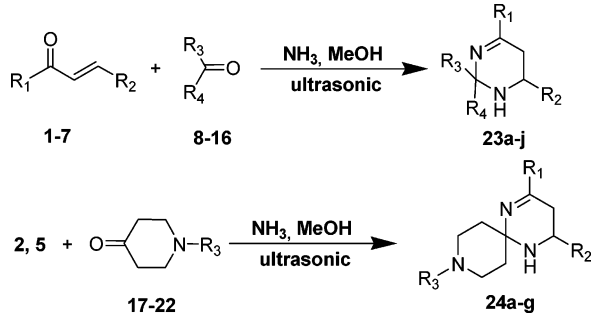
[a] Mixtures of diastereomeric pairs. [b] Mechanical shaking.

ecules of known biological activity[1a,b] and the presence of four readily variable diversity points, which opens extensive possibilities for the synthesis of diverse libraries.

Results and Discussion

Three-Component Synthesis of 1,2,5,6-Tetrahydropyrimidines. In the course of our investigations, we found that treatment of chalcones **1**−**7** with ammonia and aldehydes **8**−**11** and **13**−**16**, or acetone **12** under ultrasonic irradiation allowed us to obtain 1,2,5,6-tetrahydropyrimidines of type **23** as colorless solids in good to excellent yields. The cyclocondensations were performed at room temperature in a methanol solution saturated with ammonia, containing an equimolar mixture of the appropriate α,β-unsaturated ketone and carbonyl compounds under ultrasonic irradiation for 20−90 min. Out of the 63 possible products, a small library of 10 tetrahydropyrimidine derivatives **23a**−**j** (75−95%, Table 1) was rapidly generated using a set of seven 1,3-diarylprop-2-en-1-ones (**1**−**7**, diversity points R_1 and R_2) and nine carbonyl building blocks (**8**−**16**, diversity points R_3 and R_4). After irradiation in the ultrasonic bath, the reaction mixtures were allowed to stand at room temperature for 0.5−2 h, and the precipitated crystalline solids were subsequently filtered, washed with methanol, and air-dried. All heterocycles **23a**−**j** were obtained in high purity and without further purification were fully characterized by ^{1}H NMR and MS data, in addition to elemental analysis.

Scheme 1



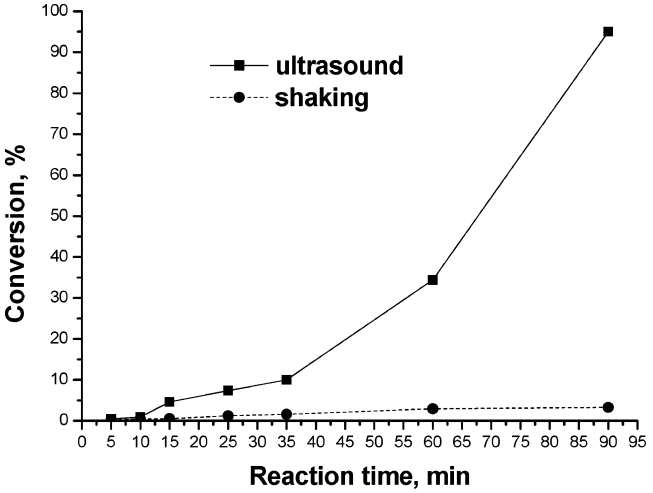
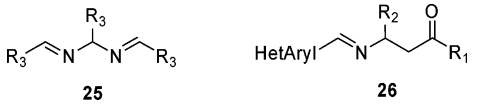


Figure 1. Reaction rates: ultrasonic vs shaking.

The reaction progress was monitored by HPLC. To determine the influence of ultrasonic irradiation on the rate of the process, we also carried out and monitored cyclocondensations with conventional shaking with orbital shaker. It was found that initial (5 min) amounts of the starting α,β-unsaturated ketone and product were similar in both cases: ultrasound irradiation and shaking. However, after 90 min of ultrasound exposure, we observed almost complete conversion of the starting materials to tetrahydropyrimidines, whereas in the case of shaking, the conversion was much lower. A very similar situation was found when we compared sonication and magnetic stirring. A plot of the reaction rates based on HPLC data for compound **23b** is shown in Figure 1As indicated in our previous investigation,[3] in many cases, the three-component reaction carried out without ultrasonic activation had a heterogeneous character, low yields, and led to the formation of 1-aryl-*N*,*N*′-bis(aryliden)methanediamines **25** (Chart 1) as competitive products.

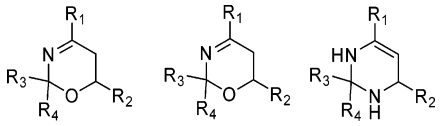
Application of sonication practically avoided the formation of byproducts and allowed the isolation of target compounds in high yield, even in case of poorly dissolving starting materials (unsaturated ketones **1**, **4**, and **5**).

Chart 1. Competitive Reaction Products



25 **26**

Chart 2. Possible Reaction Products



27 **28** **29**

Ultrasonic irradiation also significantly expanded the possibilities of this three-component reaction. The use of some heterocyclic aldehydes in case of mechanical shaking led to formation of 1,3-diaryl-3-[(hetaryl-2-ylmethylene)-amino]propan-1-ones **26** (Chart 1).[3b] However, the use of ultrasonic irradiation in the reactions of heterocyclic aldehydes **13**−**16** with the appropriate chalcones and ammonia yielded the target 1,2,5,6-tetrahydropyrimidines **23f**−**j** in good yields (75−90%).

γ-Pyridones can also be used as carbonyl components to synthesize appropriate tetrahydropyrimidines using ultrasonic activation. It was found that the three-component reaction of ketones **17**−**22** with chalcones **2** and **7** in methanol saturated with ammonia under sonication rapidly yielded 2,4-diaryl-1,5,9-triazaspiro[5.5]undec-1-enes **24a**−**g**.

Structure Elucidations. The structures of the heterocycles **23** and **24** were established by MS and NMR spectral data, as well as by X-ray analysis. The generation of several compounds and their isomers, for example, **23 (24)** and **27**−**29** (Chart 2), is possible using the method described above. Structures **27** and **28** were declined according to data of elemental analysis and MS spectra.

A choice between structures **29** and **23 (24)** initially was made on the basis of the ^{1}H NMR spectra, which exhibit the following signals: characteristic signals for the aromatic and piperidine rings (for compounds **24**), two multiplets of the CH_2 group at 2.5−2.8 and 3.1−3.5 ppm, broad singlets of H atoms in positions 6 (4.3−4.8 ppm) and 2 (4.0−5.8 ppm for compounds **23**) of the heterocycle. Signals of amino, hydroxyl, and all other functional groups are also present in the spectra at appropriate positions. Hence, the spectral data of the synthesized compounds correspond to structures **23** and **24**. The proton spin−spin decoupling experiments and COSY tetrahydropyrimidines **23a**−**d** and **f**−**j** demonstrated the presence of a long-range interaction between the H atoms in positions 2 and 5, as described in our previous publication.[3a]

Ultimately, the structures of the tetrahydropyrimidines synthesized were established on the basis of an X-ray analysis which demonstrated that **23j** has the structure of 4,6-di(2-hydroxyphenyl)-2-(pyridin-2-yl)-1,2,5,6-tetrahydropyrimidine (Figure 2).

According to the X-ray data, the structure of the compound **23j** can be described as superposition of two enatiomers (C and D) in C/D ratio of 70:30%. In both stereoisomers, the tetrahydropyrimidine ring adopts a half-chair conformation. Deviations of the N(1) and C(4) atoms from the mean plane of remaining atoms of the ring in isomer C are 0.37 and −0.22 Å, respectively, and the deviations of the N(2) and C(2) atoms in isomer D are 0.33 and −0.23 Å, respectively. The pyridine ring has a pseudoequatorial orientation (the C(2)−N(2a)−C(1)−C(11) torsion angle is 142.5(2)°), and it is turned relative to the N(2a)−C(1) bond (the N(2a)−C(1)−C(11)−N(3) torsion angle is −74.2(2)°). This position of the pyridine ring is stabilized by attractive interactions: H(1Na)···N(3) = 2.42 Å in C and H(2Nb)···N(3) = 2.26 Å in D (the sum of the corresponding van der Waals radii[9a] is 2.67 Å). Both hydroxyphenyl substituents are almost coplanar to the N=C−C−C fragment of the tetrahydropyrimidine ring (the C(3)−C(4)−C(5)−C(6) and C(3)−C(2)−C(16)−C(21) torsion angles are −7.5(3) and 7.8(3)°, respectively), despite the repulsion between phenyl ring and heterocycle (the shortened intramolecular contacts H(3a)···C(6)= 2.82 Å, H(3b)···C(21) = 2.76 Å, H(6)···C(3) = 2.56 Å, H(21)···C(3) = 2.58 Å; the sum of the corresponding van der Waals radii is 2.87 Å). It can be assumed that such orientation of these substituents are caused by the existence of the intramolecular hydrogen bonds: O(1)−H(1O)···N(1a) H···N = 1.90 Å, O−H···N = 146°; O(1)−H(1O)···N(1b) H···N = 1.82 Å, O−H···N = 144° in C and O(2)−H(2O)···N(2a) H···N = 1.80 Å, O−H···N 147°; O(2)−H(2O)···N(2b) H···N = 1.88 Å, O−H···N = 145° in D.

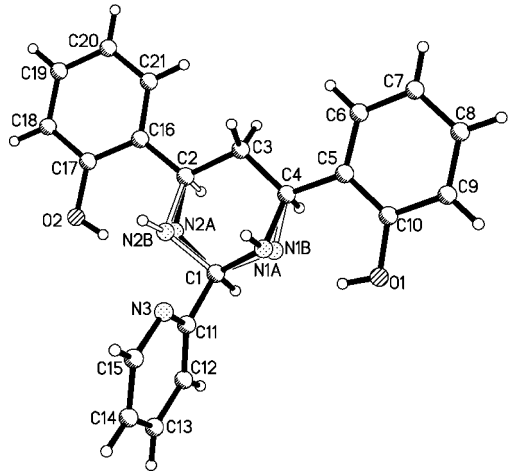


Figure 2. Molecular structure (X-ray diffraction data) of compound **23j**.

According to the ^{1}H NMR spectra containing two sets of identical signals, the tetrahydropyrimidines **23c**, **d**, **f**, and **g** were found to be mixtures of diastereomeric pairs caused by the presence of two stereogenic centers. The amount of a minor diastereomer could vary in a wide range (see Experimental section). The relative configurations of the stereogenic centers for both possible diastereomers **A** and **B** were established with help of NOE experiments: the presence of NOE between $C_{(2)}H$ and $C_{(6)}H$ confirms that the major diastereomer **A** has a *trans* orientation of appropriate aryl substituents, while the minor isomer **B** is situated in a *cis* configuration (Figure 3). Compounds **23b** and **h**−**j** were isolated only as *trans* isomer **A**.

Biological Screening of the Tetrahydropyrimidines. The primary biological screening of tetrahydropyrimidines obtained in this work, as well as in a previous publication,[3a] was realized by the U.S. National Institute of Allergy and Infectious Diseases against *Mycobacterium tuberculosis*

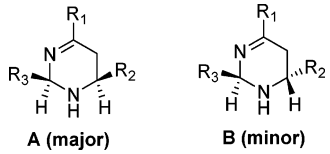


Figure 3. Relative configuration of diastereomers of compounds **23**.

strain $H_{37}Rv$ (ATCC 27294) at the single concentration of 6.25 μg/mL in BATEC 12B medium using a broth microdilution assay, Micropalte Alamar Blue Assay (MABA).[7] The majority of the compounds had an inhibitory activity within 50−80%. However, compound **23d** possessed 98% activity against *M. tuberculosis* and should be evaluated for further in vitro tests, like the determination of the actual minimum of inhibitory concentration (MIC), cytotoxicity (IC_{50}), etc.

Some compounds of the tetrahydropyrimidine type, including **23c**, **j**, and **24g**, **f**, were also selected by U.S. National Cancer Institute for anticancer activity tests.

Conclusions

We have developed a fast and convenient ultrasonic-promoted procedure for the rapid generation of 2-aryl-(hetaryl)-4,6-diaryl-1,2,5,6-tetrahydropyrimidines **23** and 2,4-diaryl-1,5,9-triazaspiro[5.5]undec-1-enes **24** by three-component reaction of α,β-unsaturated ketones, carbonyl compounds, and ammonia. In contrast to the conventional mechanical shaking method, requiring about 48 h, sonicated reactions were completed within 90 min of ultrasonic irradiation at room temperature and provided the desired products in high yields and purities. The primary biological screening showed 98% inhibitory activity against *Mycobacterium tuberculosis* by compound **23d**.

Experimental Section

General. The melting points of all compounds synthesized were determined with a Kofler apparatus and are uncorrected. The NMR spectra were recorded in DMSO-d_6 at 200 MHz (50 MHz for 13C) on a Varian Mercury VX-200 spectrometer. The MS spectra were measured on a GC-MS Varian 1200L instrument (EI, ionizing voltage 70 eV). Elemental analysis was performed on a EuroVector EA-3000. HPLC experiments were performed on Bischoff module chromatograph on RP C-18 column using a 45% acetonitrile/water mixture as eluent.

Sonication was carried out with help of a standard ultrasonic bath (produced by SELDI, Ukraine), producing irradiation at 44.2 kHz.

The synthesis of chalcones and *o*-hydroxychalcones was carried out by the conventional methods[8] from substituted aldehydes and appropriate acetophenones.

X-ray Diffraction Study. Crystals of **22j** are monoclinic. At the 293 K, $a = 11.448(5)$ Å, $b = 11.321(5)$ Å, $c = 14.176(5)$ Å, $\beta = 110.51(4)°$, $V = 1721(1)$ Å^3, $M_r = 345.39$, $Z = 4$, space group $P2_1/c$, $d_{calcd} = 1.333$ g/cm^3, μ(Mo Kα) = 0.088 mm^{-1}, $F(000) = 728$. The intensities of 8728 reflections (2995 independent, $R_{int} = 0.080$) were measured on the Xcalibur-3 diffractometer (graphite-monochromated Mo Kα radiation, CCD detector, ω-scans, $2\Theta_{max} = 50°$). The structure was solved by direct method using the SHELXTL package[9b]. During refinement, some constraints were applied for the bond lengths in the tetrahydropyrimidine ring: $Csp^2{=}N(2) = 1.30(1)$ Å, $Csp^3{-}N(1) = 1.46(1)$ Å, $Csp^3{-}N(3) = 1.47(1)$ Å. The positions of hydrogen atoms were located from electron density difference maps and refined by a "riding" model with $U_{iso} = nU_{eq}$ of the non-hydrogen atom bonded with given hydrogen atom ($n = 1.5$ for hydroxyl group and $n = 1.2$ for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation using 2955 reflections was converged to wR2 = 0.141 (R1 = 0.055 for 1108 reflections with $F > 4\sigma(F)$), $S = 0.771$). Atomic coordinates and crystallographic parameters have been deposited with the Cambridge Crystallographic Data Centre (CCDC 644890; http://www.ccdc.cam.ac.uk/).

Ultrasonic-Promoted Synthesis of 1,2,5,6-Terahydropyrimidines 23 and 24. General Procedure. A mixture of the appropriate α,β-unsaturated ketone **1**−**7** (0.1 mmol) and the carbonyl compound **8**−**22** (0.1 mmol) in methanol saturated with ammonia (2 mL) was sonicated at room temperature for 90 min in a round-bottom flask equipped with condenser. The reaction mixture was allowed to stand for 0.5−2 h at room temperature and was then filtered to give the solid tetrahydropyrimidine products **23a**−**j and 24a**−**g**, which were washed with methanol and dried in air. The reaction products were obtained in high purity (>98% by ^{1}H NMR) and did not require further purification by recrystallization. The analytical samples were dried in a drying pistol.

Conventional Synthesis of 1,2,5,6-Tetrahydropyrimidines 23 and 24. General Procedure. A mixture of the appropriate α,β-unsaturated ketone **2**, **4**, or **5** (0.1 mmol) and the carbonyl compound **9**, **11**, or **12** (0.1 mmol) in methanol saturated with ammonia (2 mL) was shaken with orbital shaker (or stirred on magnetic stirrer) at room temperature for 48 h in a sealed conical flask. The reaction mixture was filtered to give the solid tetrahydropyrimidine products **23b**, **d**, and **e**, which were washed with methanol. The reaction products were crystallized from propan-2-ol and dried in air.

4-(2-Hydroxyphenyl)-6-(4-fluorophenyl)-1,2,5,6-tetrahydropyrimidine (23a). Yellowish prisms. mp: 111−112 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.57 (m, 1 H, 5-CH), 3.01 (m, 1H, NH), 3.19 (m, 1 H, 5-CH), 4.03 (m, 1 H, 2-CH), 4.65 (m, 1 H, 2-CH), 4.79 (m, 1 H, 6-CH), 6.75 − 7.63 (m, 8 H_{arom}), 15.31 (s, 1 H, OH). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 32.9, 52.6, 63.5, 115.3, 115.5, 117.8, 119.5, 127.7, 132.5, 140.0, 160.7, 162.0, 162.7, 170.1. MS (EI, 70 eV): *m*/*z* (%) 270 (100) [M$^+$], 240 (43.3), 147 (93.8), 146 (43.2). Anal. Calcd for $C_{16}H_{15}FN_2O$ (%): C, 71.10; H, 5.59; N, 10.36. Found: C, 71.19; H, 5.66; N, 10.33.

2,4-Diphenyl-6-(2-hydroxyphenyl)-1,2,5,6-tetrahydropyrimidine (23b). Yellowish prisms. mp: 160−161 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.64 (m, 1 H,5- CH), 3.13 (m, 1H, NH), 3.27 (m, 1H, 5-CH), 4.39 (m,1 H, 6-CH), 5.66 (m, 1 H, 2-CH), 6.76 − 7.96 (m, 14 H_{arom}), 10.38 (s, 1 H, OH). MS (EI, 70 eV): *m*/*z* (%) 328 (10.3) [M$^+$], 208 (33.2), 207 (27), 120 (38.4), 106 (97.2), 104 (100), 91 (50.1). Anal.

Calcd for $C_{22}H_{20}N_2O$ (%): C, 80.46; H, 6.14; N, 8.53. Found: C, 80.40, H, 6.20; N, 8.50.

2-(4-Chlorophenyl)-4-(2-hydroxyphenyl)-6-(3-pyridinyl)-1,2,5,6-tetrahydropyrimidine (23c). Yellowish prisms of two diastereomeric pairs A (84%) and B (16%). ^{1}H NMR (DMSO-d_6, 200 MHz, A (B)): δ 2.76 (m, 1 H, 5-CH), 3.23 (m, 1 H, NH), 3.27 (m, 1 H, 5-CH), 4.35 (3.92) (m, 1 H, 6-CH), 5.79 (5.94) (m, 1 H, 2-CH), 6.80−8.73 (m, 12 H_{arom}), 15.13 (15.32) (s, 1 H, OH). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 32.8, 52.6, 74.3, 117.8, 118.4, 124.0, 128.4, 128.8, 129.4, 129.5, 132.9, 134.6, 134.8, 138.9, 141.4, 148.8, 148.9, 161.9, 170.8. MS (EI, 70 eV): *m*/*z* (%) 363 (26.3) [M^+], 259 (19.7), 231 (27.3), 229 (100.0), 223 (29.4), 167 (13.3). Anal. Calcd for $C_{21}H_{18}ClN_3O$ (%): C, 69.32; H, 4.99; N, 11.55. Found: C, 69.39; H, 5.07; N, 11.58.

4-(1,3-Benzodioxol-5-yl)-2-(4-bromophenyl)-6-(2-hydroxy-5-chlorophenyl)-1,2,5,6-tetrahydro-pyrimidine (23d). Yellowish prisms of two diastereomeric pairs A (90%) and B (10%). ^{1}H NMR (DMSO-d_6, 200 MHz, A (B)): δ 2.54 (m, 1 H, 5-CH), 3.01 (m, 1 H, NH), 3.14 (m, 1 H, 5-CH), 4.35 (4.47) (m, 1 H, 6-CH), 5.61 (5.71) (m, 1 H, 2-CH), 6.06 (bs, 2H, CH_2O_2), 6.78−7.65 (m, 12 H_{arom}), 10.28 (bs, 1 H, OH). MS (EI, 70 eV): *m*/*z* (%) 486 (4.1) [M^+], 185 (26.6), 184 (48.3), 182 (48.1), 155 (50), 148 (59.1), 104 (20.9), 103 (40.5), 89 (100). Anal. Calcd for $C_{23}H_{18}ClBrN_2O_3$ (%): C, 56.87; H, 3.74; N, 5.77. Found: C, 56.80; H, 3.69; N, 5.74.

2,2-Dimethyl-6-(2-hydroxyphenyl)-4-(4-methylphenyl)-1,2,5,6-tetrahydropyrimidine (23e). Colorless prisms. mp: 173−174 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.39 (s, 3 H, 2-CH_3), 1.40 (s, 3 H, 2-CH_3), 2.31 (s, 3 H, CH_3), 2.39 (m, 1 H, 5-CH), 2.98 (m, 1 H, NH), 3.26 (m, 1 H, 5-CH), 4.28 (m,1 H, 6-CH), 6.71−7.77 (m, 8 H_{arom}), 10.96 (s, 1 H, OH). MS (EI, 70 eV): *m*/*z* (%) 294 (8.6) [M^+], 174 (40.5), 173 (49.2), 121 (28.7), 120 (69.2), 117 (50.2), 115 (31.6), 91 (100). Anal. Calcd for $C_{19}H_{22}N_2O$ (%): C, 77.52; H, 7.53; N, 9.52. Found: C, 77.48; H, 7.59; N, 9.50.

6-(2-Hydroxy-5-chlorophenyl)-4-phenyl-2-(3-thienyl)-1,2,5,6-tetrahydropyrimidine (23f). Yellowish prisms of two diastereomeric pairs A (70%) and B (30%). ^{1}H NMR (DMSO-d_6, 200 MHz, A (B)): δ 2.58 (m, 1 H, 5-CH), 3.09 (m, 1 H, NH), 3.44 (3.67) (m, 1 H, 5-CH), 4.35 (4.02) (m, 1 H, 2-CH), 5.69 (5.94) (m, 1 H, 6-CH), 6.74−7.95 (m, 11 H_{arom}), 10.42 (s, 1 H, OH). MS (EI, 70 eV): *m*/*z* (%) 368 (5.3) [M^+], 257 (22.7), 242 (27.7), 241 (32.6), 240 (100.0), 214 (96.1). Anal. Calcd for $C_{20}H_{17}ClN_2OS$ (%): C, 65.12; H, 4.65; N, 7.52. Found: C, 65.18; H, 4.71; N, 7.54.

4,6-Di(2-hydroxyphenyl)-2-(2-thienyl)-1,2,5,6-tetrahydropyrimidine (23g). Colorless prisms of two diastereomeric pairs A (72%) and B (28%). ^{1}H NMR (DMSO-d_6, 200 MHz, A (B)): δ 2.62 (m, 1 H, 5-CH), 3.13 (m, 1 H, NH), 3.45 (3.80) (m, 1 H, 5-CH), 4.42 (4.13) (m, 1 H, 6-CH), 5.96 (6.10) (m, 1 H, 2-CH), 6.76−7.62 (m, 11 H_{arom}), 9.9 (9.76) (s, 1 H, OH), 14.87 (15.06) (s, 1 H, OH). MS (EI, 70 eV): *m*/*z* (%) 350 (57.2) [M^+], 230 (22.3), 229 (44.8), 222 (95.2), 216 (100.0). Anal. Calcd for $C_{20}H_{18}N_2O_2S$ (%): C, 68.55; H, 5.18; N, 7.99. Found: C, 68.49; H, 5.13; N, 7.97.

6-(2-Hydroxyphenyl)-4-phenyl-2-(2-thienyl)-1,2,5,6-tetrahydropyrimidine (23h). Colorless prisms. mp: 160−161 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.61 (m, 1 H, 5-CH), 3.08 (m, 1 H, NH), 3.37 (m, 1 H, 5-CH), 4.39 (m, 1 H, 6-CH), 5.86 (m, 1 H, 2-CH), 6.82−7.91 (m, 12 H_{arom}), 10.14 (s, 1 H, OH). MS (EI, 70 eV): *m*/*z* (%) 334 (18.8) [M^+], 223 (44.5), 222 (20.7), 214 (75.6), 213 (29.7), 206 (100.0). Anal. Calcd for $C_{20}H_{18}N_2OS$ (%): C, 71.83; H, 5.42; N, 8.38. Found: C, 71.87; H, 5.39; N, 8.35.

6-(2-Hydroxyphenyl)-2-[2-(3-methylthienyl)]-4-phenyl-1,2,5,6-tetrahydropyrimidine (23i). Colorless prisms. mp: 155−156 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.31 (s, 3 H, CH_3), 2.61 (m, 1 H, 5-CH), 3.09 (m, 1 H, NH), 3.26 (m, 1 H, 5-CH), 4.37 (m, 1 H, 6-CH), 5.92 (m, 1 H, 2-CH), 6.76 − 7.94 (m, 12 H_{arom}), 10.34 (s, 1 H, OH). MS (EI, 70 eV): *m*/*z* (%) 348(6.9) [M^+], 228 (25.4), 223 (27.2), 208 (30), 207 (100), 206 (26.8). Anal. Calcd for $C_{21}H_{20}N_2OS$ (%): C, 72.38; H, 5.79; N, 8.04. Found: C, 72.34; H, 5.86; N, 8.07.

4,6-Di(2-hydroxyphenyl)-2-(2-pyridinyl)-1,2,5,6-tetrahydropyrimidine (23j). Colorless prisms. mp: 189−190 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.79 (m, 1 H, 5-CH), 3.20 (m, 1 H, NH), 3.49 (m, 1 H, 5-CH), 4.46 (m, 1 H, 6-CH), 5.86 (m, 1 H, 2-CH), 6.76−8.60 (m, 12 H_{arom}), 10.02 (s, 1 H, OH), 15.15 (s, 1 H, OH). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 31.1, 51.1, 75.5, 116.0, 117.8, 118.3, 119.4, 119.6, 122.1, 122.6, 123.8, 127.0, 127.8, 128.1, 128.6, 132.8, 137.8, 149.5, 155.8, 159.9, 161.9, 170.6. MS (EI, 70 eV): *m*/*z* (%) 345 (61.0) [M^+], 225 (49.9), 224 (100.0), 222 (66.2), 211 (68.9), 209 (30.4). Anal. Calcd. for $C_{21}H_{19}N_3O_2$ (%): C, 73.03; H, 5.54; N, 12.17. Found: C, 73.08; H, 5.59; N, 12.15.

9-Benzyl-4-(2-hydroxyphenyl)-2-phenyl-1,5,9-triazaspiro-[5.5]undec-1-ene (24a). Yellow prisms. mp: 174−175 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.72−1.95 (m, 4 H, 7-CH_2 and 11-CH_2), 2.52 (m, 1 H, 3-CH), 2.59−2.75 (m, 4 H, 8-CH_2 and 10-CH_2), 3.02 (m, 1 H, NH), 3.11 (m, 1 H, 3-CH), 3.53 (s, 2 H, N−CH_2), 4.29 (m, 1 H, 4-CH), 6.74−7.43 (m, 14 H_{arom}), 11.10 (s, 1 H, OH). MS (EI, 70 eV): *m*/*z* (%) 411 (75.0) [M^+], 292 (100.0), 291 (26.0), 289 (54.8). Anal. Calcd for $C_{27}H_{29}N_3O$ (%): C, 78.80; H, 7.10; N, 10.21. Found: C, 78.75; H, 7.15; N, 10.20.

2,4-Di(2-hydroxyphenyl)-9-isopropyl-1,5,9-triazaspiro-[5.5]undec-1-ene (24b). Colorless prisms. mp: 239−240 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 0.98 (d, J = 6,3 Hz, 3 H, CH_3), 1.02 (d, J = 6,3 Hz, 3 H, CH_3), 1.75−2.03 (m, 4 H, 7-CH_2 and 11-CH_2), 2.52 (m, 1 H, 3-CH), 2.57−2.67 (m, 4 H, 8-CH_2 and 10-CH_2), 2.74 (m, 1H, N−CH), 3.16 (m, 1 H, NH), 3.27 (m, 1 H, 3-CH), 4.41 (m, 1 H, 4-CH), 6.76−7.71 (m, 8 H_{arom}), 10.59 (s, 1 H, OH), 15.62 (s, 1 H, OH). MS (EI, 70 eV): *m*/*z* (%) 379 (47.4) [M^+], 244 (46.6), 174 (20.4), 139 (35.9), 125 (45.5), 124 (52.1), 120 (49), 100 (44.5), 99 (100), 98 (50.7). Anal. Calcd for $C_{23}H_{29}N_3O_2$ (%): C, 72.79; H, 7.70; N, 11.07. Found: C, 72.70; H, 7.67; N, 11.10.

2,4-Di(2-hydroxyphenyl)-9-methyl-1,5,9-triazaspiro-[5.5]-undec-1-ene (24c). Colorless prisms. mp: 223−225 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.75−2.08 (m, 4 H, 7-CH_2 and 11-CH_2), 2.21 (s, 3H, CH_3), 2.25−2.49 (m, 4 H, 8-CH_2 and 10-CH_2), 2.62 (m, 1 H, 3-CH), 3.17 (m, 1 H, NH), 3.25 (m, 1 H, 3-CH), 4.43 (m, 1 H, 4-CH), 6.77−7.72 (m, 8 H_{arom}), 10.53 (s, 1 H, OH), 15.61 (s, 1 H, OH). MS (EI, 70 eV): *m*/*z* (%) 351 (54.4) [M^+], 231 (21.4), 229 (41.5),

222 (25.6), 216 (100.0). Anal. Calcd for $C_{21}H_{25}N_3O_2$ (%): C, 71.77; H, 7.17; N, 11.96. Found: C, 71.70; H, 7.22; N, 11.94.

2,4-Di(2-hydroxyphenyl)-9-ethyl-1,5,9-triazaspiro[5.5]-undec-1-ene (24d). Colorless prisms. mp: 206−208 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.02 (t, J = 7,7 Hz, 3 H, CH_3), 1.76−2.03 (m, 4 H, 7-CH_2 and 11-CH_2), 2.38 (q, J = 7,7 Hz, 2 H, CH_2), 2.50−2.62 (m, 4 H, 8-CH_2 and 10-CH_2), 2.65 (m, 1 H, 3-CH), 3.17 (m, 1 H, NH), 3.22 (m, 1 H, 3-CH), 4.42 (m,1 H, 4-CH), 6.76−7.72 (m, 8 H_{arom}), 10.56 (s, 1 H, OH), 15.61 (s, 1 H, OH). MS (EI, 70 eV): *m*/*z* (%) 365 (8.4) [M^+], 222 (100). Anal. Calcd for $C_{22}H_{27}N_3O_2$ (%): C, 72.30; H, 7.45; N, 11.50. Found: C, 72.26; H, 7.40; N, 11.48.

2,4-Di(2-hydroxyphenyl)-9-carbethoxy-1,5,9-triazaspiro-[5.5]-undec-1-ene (24e). Colorless prisms. mp: 176−177 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.19 (t, J = 7,3 Hz, 3 H, CH_3), 1.73−1.96 (m, 4 H, 7-CH_2 and 11-CH_2), 2.61 (m, 1 H, 3-CH), 3.09 (m, 1 H, NH), 3.22 (m, 1H, 3-CH), 3.40−3.57 (m, 4 H, 8-CH_2 and 10-CH_2), 4.06 (q, J = 7,3 Hz, 2 H, CH_2O), 4.41 (m, 1 H, 4-CH), 6.78−7.69 (m, 8 H_{arom}), 10.18 (s, 1 H, OH), 15.46 (s, 1 H, OH). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 15.1, 30.9, 35.6, 38.7, 45.2, 61.3, 70.3, 116.0, 117.9, 118.3, 119.3, 119.5, 127.6, 128.2, 128.4, 128.6, 132.8, 155.2, 156.1, 162.1, 169.5. MS (EI, 70 eV): *m*/*z* (%) 409 (12.2) [M^+], 275 (49.5), 274 (56.4), 222 (100.0), 171 (25.7). Anal. Calcd for $C_{23}H_{27}N_3O_4$ (%): C, 67.46; H, 6.65; N, 10.26. Found: C, 67.49; H, 6.59; N, 10.24.

9-Acetyl-2,4-di(2-hydroxyphenyl)-1,5,9-triazaspiro[5.5]-undec-1-ene (24f). Colorless prisms. mp: 215−218 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.71−1.98 (m, 4 H, 7-CH_2 and 11-CH_2), 2.04 (s, 3 H, CH_3), 2.61 (m, 1 H, 3-CH), 3.10 (m, 1 H, NH), 3.24 (m, 1 H, 3-CH), 3.40−3.64 (m, 4 H, 8-CH_2 and 10-CH_2), 4.43 (m, 1 H, 4-CH), 6.78−7.70 (m, 8 H_{arom}), 10.23 (s, 1 H, OH), 15.46 (s, 1 H, OH). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 21.9, 30.8, 35.5, 37.6, 45.2, 70.4, 116.0, 117.8, 118.3, 119.4, 119.5, 127.0, 128.2, 128.4, 128.6, 132.7, 156.2, 162.1, 168.8, 169.5 MS (EI, 70 eV): *m*/*z* (%) 379(19.2) [M^+], 222 (100.0), 244 (92.2), 258 (34.0), 223 (24.6). Anal. Calcd for $C_{22}H_{25}N_3O_3$ (%): C, 69.64; H, 6.64; N, 11.07. Found: C, 69.60; H, 6.69; N, 11.05.

9-Benzyl-2,4-di(2-hydroxyphenyl)-1,5,9-triazaspiro[5.5]-undec-1-ene (24g). Colorless prisms. mp: 223−224 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.72−2.07 (m, 4 H, 7-CH_2 and 11-CH_2), 2.50−2.61 (m, 4 H, 8-CH_2 and 10-CH_2), 2.65 (m, 1 H, 3-CH), 3.17 (m, 1 H, NH), 3.24 (m, 1 H, 3-CH), 3.51 (s, 2 H, N−CH_2), 4.41 (m, 1 H, 4-CH), 6.70−7.70 (m, 8 H_{arom}), 10.51 (s, 1 H, OH), 15.63 (s, 1 H, OH). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 30.6, 45.6, 49.6, 50.0, 62.7, 70.1, 116.1, 117.8, 118.1, 119.4, 127.4, 127.5, 128.1, 128.2, 128.6, 128.7, 128.8, 129.2, 132.6, 139.2, 156.6, 162.3, 168.7. MS (EI, 70 eV): *m*/*z* (%) 427(47.0) [M^+], 336 (19.6). 292 (100.0), 201 (32.7), 187 (54.9). Anal. Calcd for $C_{27}H_{29}N_3O_2$ (%): C, 75.85; H, 6.84; N, 9.83. Found: C, 75.80; H, 6.79; N, 9.86.

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