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Synthesis of 7- Methyl-6-indolopterin and 7- Methyl-6-indoloquinoxaline

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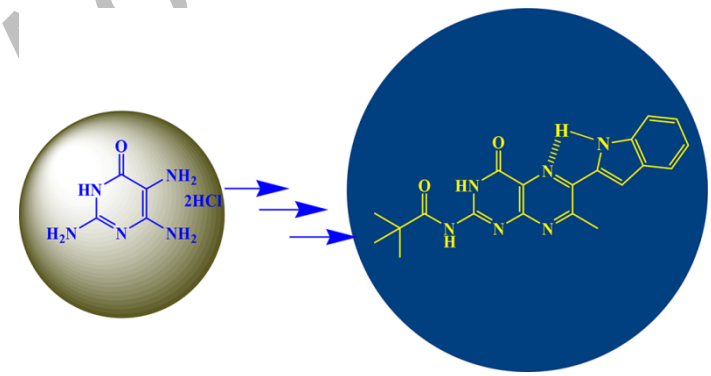
Abstract

First synthesis of indolopterin and indoloquinoxaline, two new important dissimilar diheterocycles linking C-2 of indole with C-6 of pterin (significant position for showing biological activity) and quinoxaline respectively has been achieved based on two famous classic reactions. The introduction of keto methyl group onto the 6-position of pterin and quinoxaline by several steps followed by Fischer indole synthesis led to these target dissimilar diheterocycles. These indole substituted diheterocycles will significantly increase the electron density on the pterin-5-N and quinoxazoline-2-N which may change the redox properties of pterin and quinoxaline and also the electron withdrawing pterin or quinoxazoline should make the indole NH more acidic.

Graphical abstract



KEYWORDS: Pterin, indole, quinoxaline, indolopterin, indoloquinoxaline

INTRODUCTION

Pterin is one of the most important heterocyclic compounds containing bicyclic ring system. The most well-known compounds, pterins and folates are derived from pterin. Pterins are those compounds which posses the additional functional groups bonded to pyrazine subring. On the other hand, the conjugated pterins containing p-aminobenzoic acid and L-glutamates are called folates. These are the most significant compounds in large number of natural and biological group transfer reactions.[1–8] The fused heteroaromatic coenzymes originating from guanosine are called pterins which are also ubiquitous and highly redox-active molecules.[9] From the physiological point of view, the investigation of pterins is their correlations to several diseases, including hematological neoplasias,[10] sudden infant death syndrome[11] etc. Now, methotrexate, an important anti-leukemia drug and the folic acid, a significant nutrient and vitamin (vitamin B9) are also derived from pterins.

The existence of pterin moiety[12,13] in molybdenum cofactor also gives us a visible evidence of its importance in medicinal chemistry. Indole is also a hetero-bicyclic compound containing the six-membered benzene ring fused with five-membered pyrrole ring. Indole is the essential constituent of fragrances and it can take part as the precursor of many pharmaceuticals.[14] Indole-derived compounds are also of significance in natural product chemistry and pharmacology.[15] In alkaloid chemistry, on the other hand, indole has the significant role and many indole alkaloids[16] have the important possession in

physiological activity and some of them are used in medicine. Consequently, the synthesis of indole derivatives is an essential area of research.

Now, in our laboratory, we are interested in synthesizing pterin derived new compounds of potential medicinal interest. Pterin, indole and quinoxaline are important heterocycles which have been utilized in many biologically active natural products used as a wide variety of medicines. Many designed synthetic medicines possess these heterocycles. Interestingly, most important pterin natural compounds are substituted at 6-position. Since pterin and indole both are naturally and synthetically important as they have strong relevance in medicinal chemistry, we wanted to synthesise pterin substituted by indole specifically at 6-position (6-substitution has natural and synthetic significance). Quinoxaline and their derivatives are useful as antitumor antibiotics and potent bactericides. Though 2-(2-furyl) quinoxaline is known,[17] to the best of our knowledge, indoloquioxaline or indolopterin are not known naturally or synthetically.

RESULTS AND DISCUSSION

Here we report the total synthesis of these combined heterocycles or conjugated heterocycles to be present not as fused system but as a distinct identity with making an intra-molecular H-bonding including a stable five-membered ring framework (Scheme **1,** **1f** and scheme **2**, **2d**). In the retro analysis of the synthesis of dissimilar targeted diheterocycles **1f** and **2d** originates from quick development of pterin-6-keto-methyl and quinoxaline-2-keto-methyl intermediates (**1c** and **2b**) which should allow the construction

of indole moiety by Fisher indole synthesis from the corresponding phenyl hydrazones of the corresponding keto methyl groups of pterin and quinoxaline (scheme 1) respectively.

In continuation of our work on tri and tetracarbonyl compounds[18] for the synthesis of heterocycles, the formation of 6-keto-methyl pterin ring can be conveniently achieved by the condensation of the stable tricarbonyl compound[19] **1h** with triamino-4-oxopyrimidine. The selenium dioxide oxidation (one equivalent) of acetylacetone produces the desired stable tricarbonyl compound pentane-2,3,4-trione (**1h**). Thus, the total synthesis of 7-methyl-6-indolylpterin begins from 2,5,6-triamino-4-oxo-pyrimidine (**1a**) as shown in scheme 2. The trione (**1h**) was allowed to react by Gabriel-Isay condensation[20] with the above pyrimidine (**1a**) to give rise to the synthesis of 7-methyl-6-keto-methyl pterin (**1c**) in the crude form which gave the soluble product **1d** by the action of pivalic anhydride in the presence of catalytic DMAP. The compound **1d** was then converted to the corresponding phenylhydrazone (**1e**) which undergoes Fischer indolisation to afford the yellow fluorescent target compound **1f** in good yield. Thus, we have achieved the first synthesis of indolylpterin or pterinindole (**1f**).

Reagent & Condition: (i) Na_2SO_3 and H_2O, rt, 30 min. (ii) **1h**, H_2O, rt, 8h (iii) Pivalic anhydride, DMAP (cat.), 100 ^{o}C**,** 7h (iv) phenylhydrazine, EtOH, AcOH (few drops), 70-80 ^{o}C**,** 2h (v) $ZnCl_2$, AcOH, 150 ^{o}C**,** 1-2 h.

We have also similarly synthesised another target indolylquinoxaline (**2d**) (scheme 3).

Reagent & Condition: (i) **1h**, EtOH, rt, 1-2h (ii) Phenylhydrazine, EtOH, AcOH (few drops), 70-80 °C**,** 2h (iii) $ZnCl_2$, AcOH, 150 °C**,** 1-2h.

We have been able to develop suitable single crystals for the intermediates (**2b** and **2c**) for X-ray studies. Crystallographic data are presented in Table S1 (S21). The asymmetric unit of the compound **2b** (Fig. 1a) contains two independent molecules, molecules A and B, disordered over two sets of sites corresponding to a rotation of approximately 180°, with refined site occupancies of 0.557(4) and 0.443(4) for both molecules. Overall, all molecules are close to being planar [r.m.s. deviation for all the non-H atoms = 0.0542 and 0.0638 Å (molecule A), 0.0591 and 0.0717 Å (molecule B), for the major and minor components, respectively]. Full molecule disorder has also been observed in **2c** (Fig. 1b). The molecule is disordered over two positions with occupancies of 0.615(5) and 0.385(5), exhibiting an inversion disorder. The benzene ring forms dihedral angles of 6.51 and 5.99° for the major and minor components, respectively, with the mean plane of the quinoxaline ring system. In the crystal structure, C1*B*—H1*BD*···N1*A* hydrogen bonds [Table S2 (S21)] in **2b** bridge the molecules *A* and molecules *B* into pairs (Fig. 2a, also shown in full-page size in SI, S17) and these molecule pairs are further stacked down the *c*-axis whereas the molecules in **2c** are *linked* into *a* zigzag chain (Fig. 2b, also shown in full-page size in SI, S18) along [001] *via* N1—H1*B*···N4 hydrogen bonds.

PHOTOPHYSICAL PROPERTIES

We have studied here the fluorescence experiments of **1f** (indolylpterin) and **2d** (indolylquinoxaline) in several solvents. In non-polar aprotic solvents (e.g hexane, CCl_4

and toluene) they show deep blue fluorescence including bathochromic shift (λ_{max}) respectively. Now the intensity of the blue fluorescence gradually decreases with increasing the polarity of the solvents (moderately polar aprotic). Here we also observe the compound **1f** similar emission in $CHCl_3$, CH_2Cl_2 and THF whereas the compound **2d** gives different emission spectra with decreasing λ_{max} from $CHCl_3$, to THF. Now among the polar aprotic solvents, acetone, DMF and CH_3CN show the almost similar emission spectra (yellow fluorescence) but DMSO and ethyl acetate give a blue-shifted spectra of compound **1f** (Fig. 3).

On the other hand, the compound **2d** shows the greater red-shifted emission spectra in DMSO and CH_3CN compared to other polar aprotic solvents (Fig. 4) indicating the fast ESIPT phenomenon.

In polar protic solvent such as methanol both the compounds do not show any fluorescence probably because here methanol acts as a strong H-bond donor molecule and consequently ESIPT is prevented due to possible inter-molecular H-bonding interaction with methanol (Scheme 4).[21] The fluorescence quenching by MeOH may also be enhanced by proton-coupled depopulation of the excited state due to intermolecular hydrogen bonding. Furthermore, the positive solvochromicity rather accounts for a highly polar vibrationally relaxed excited singlet state. Therefore, ESIPT phenomena depend not only on solvent polarity but also on H-bond donor and acceptor ability of the solvents.[22]

It is a very interesting fact that if we compare the fluorescence properties of the target molecule **1f** with the indole free **1f** i.e. the only 7-methyl pterin (**1i**) compound, the later one exhibits only blue fluorescence in different solvents (Fig. 5). Again, if we compare the two molecules **1f** and **1i,** it is clear that **1f** has no fluorescence in polar protic solvent methanol where as **1i** gives blue fluorescence in methanol indicating the greater importance of indole moiety connected at 6-position of pterin molecule. Therefore, the indole moiety of compound **1f** is the driving heterocyclic moiety onto pterin for solvatochromic ESIPT phenomena. On the other hand, eliminating indole moiety from compound **2d** i.e only quinoxaline methyl moiety has no naked-eye fluorescence property itself. Thus, the combination of the two dissimilar suitable heterocycles has a greater importance in modern ESIPT based research.

CONCLUSION

Thus, we have achieved the synthesis of two important dissimilar diheterocycles, indolopterin (**1f**) and indoloquinoxaline (**2d**) using Gabriel-Isay synthesis for pterin ring system followed by Fischer indole synthesis for the development of the substituted indole ring. The new system of such array of two important heterocycles has the potential of new conjugated donor-acceptor moieties having interesting solvatochromic properties and for development of other possible fluorescence markers. Further studies are in progress in our laboratory for the synthesis of new arrays of heterocycles from pterins and quinoxalines for their possibility of new biological and sensor activities.

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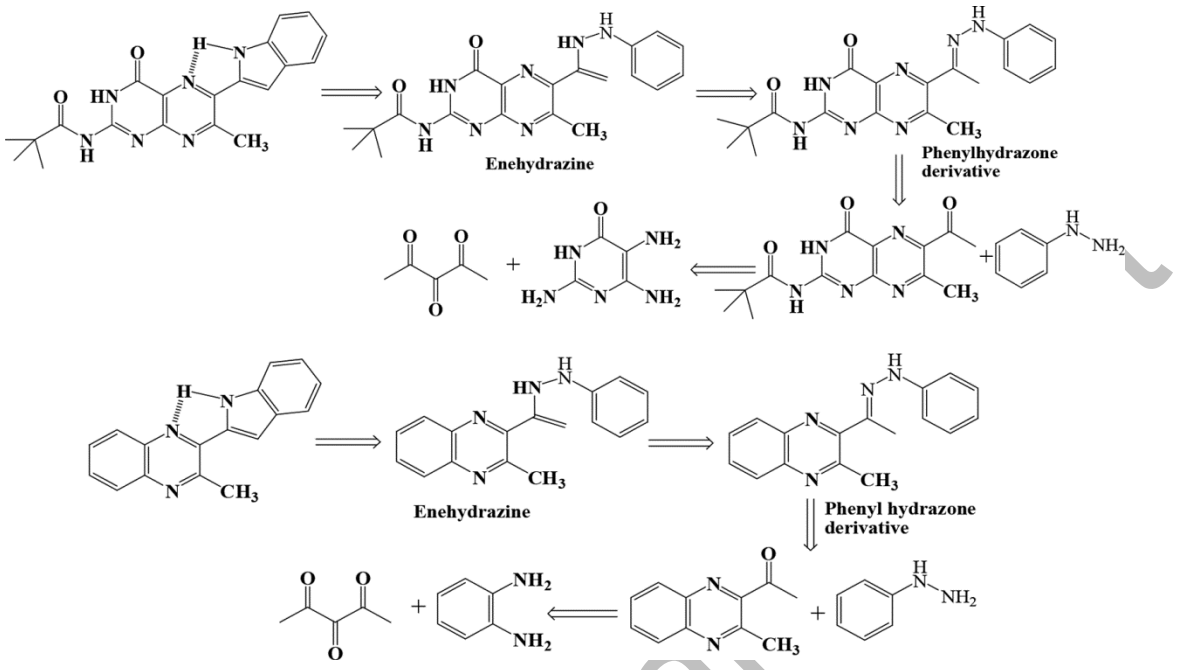
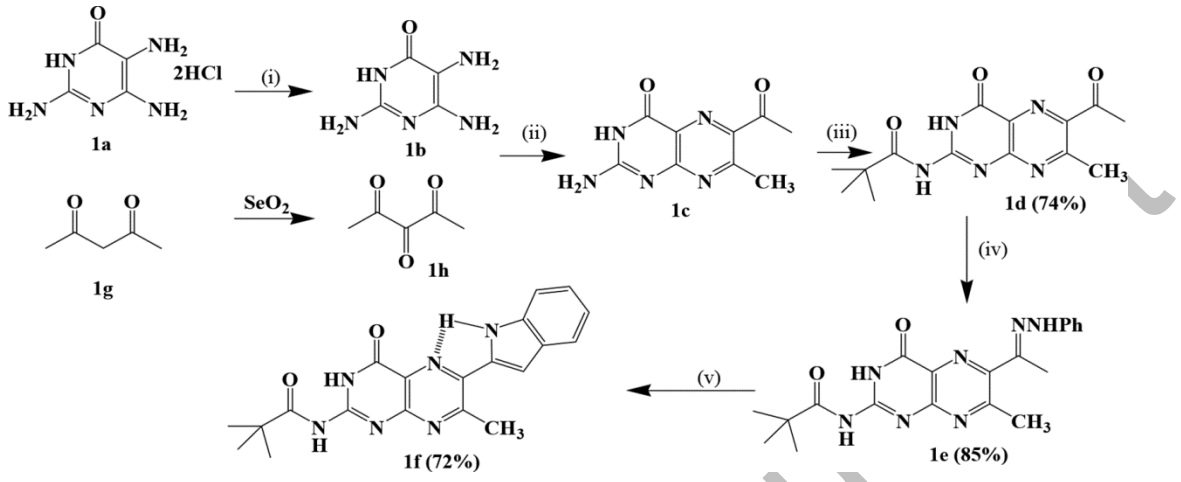
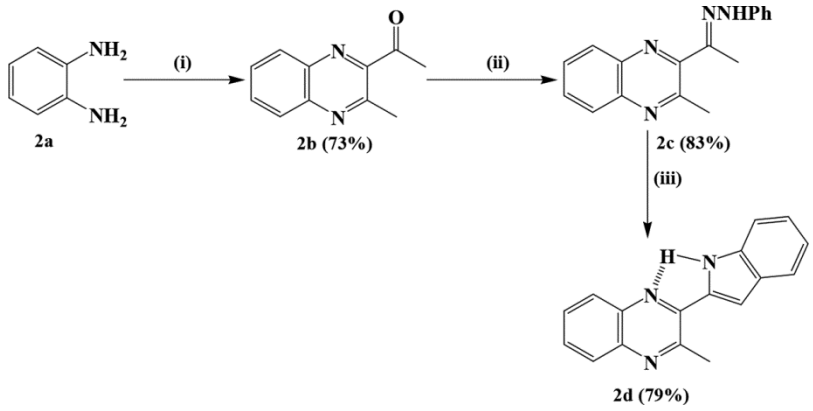
Scheme 1. Retrosynthetic route of Indolopterin and Indoloquinoxaline.



Scheme 2. Synthesis of N-[6-(1H-Indole-2-yl)-7-methyl-4-oxo-3,4-dihydro-pteridin-2-yl]-2,2-dimethyl- propionamide (**1f**).



Scheme 3. Synthesis of 2-(1H-Indole-2-yl)-3-methyl-quinoxalin (**2d**).



Scheme 4: Mechanism of ESIPT.

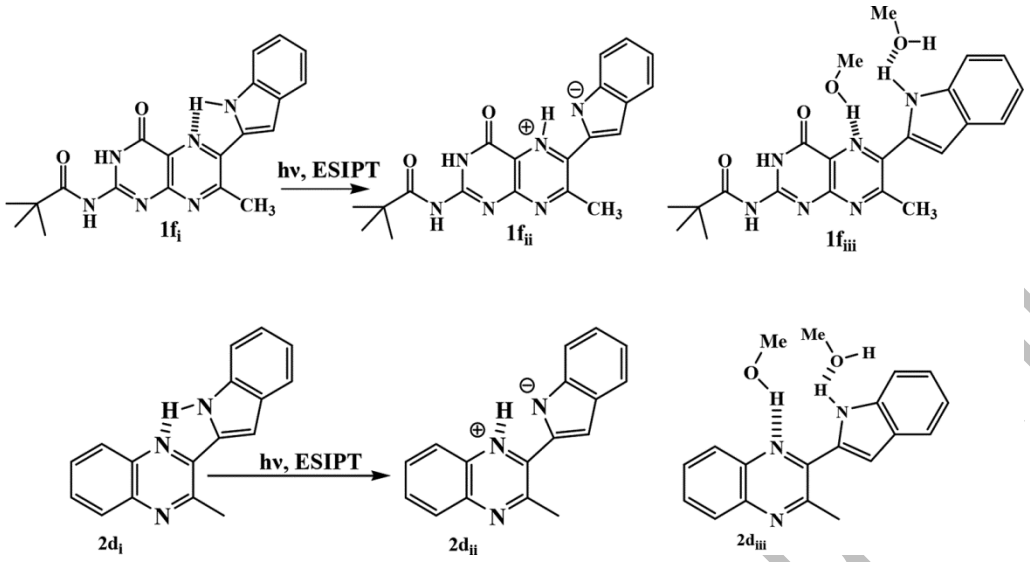
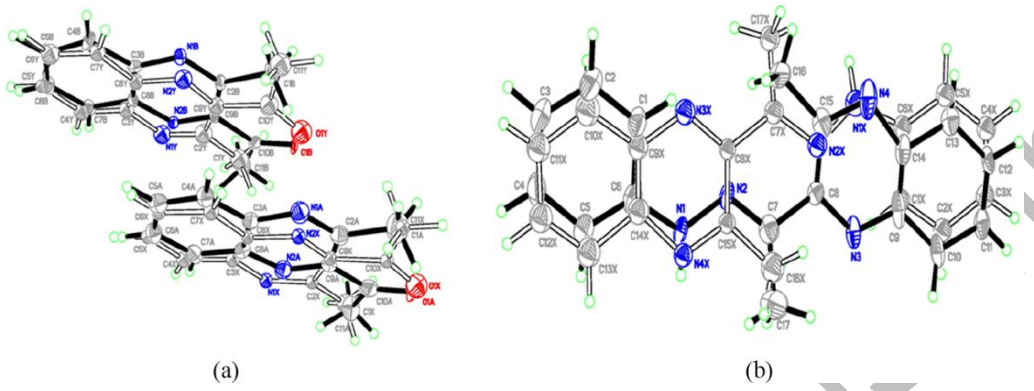
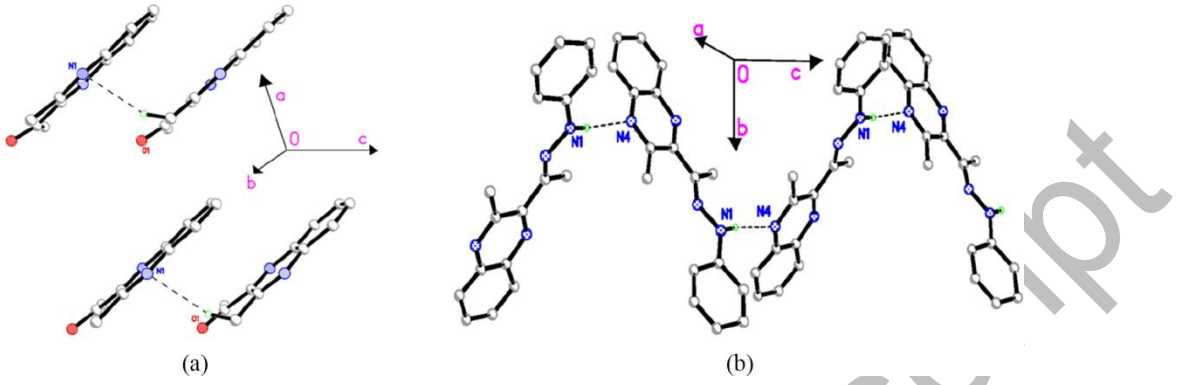


Figure 1. Molecular view of compounds (a) **2b** and (b) **2c**, with atomic numbering schemes. Both major (solid bonds) and minor (open bonds) components of the disorder are shown.



(a) (b)

Figure 2. The crystal packing of the major component of compounds (a) **2b** and (b) **2c**, viewed along the (a) *b*-axis and (b) *a*-axis.



(a) (b)

Figure 3. Comparative fluorescence of compound **1f** in different solvents at 1x 10^{-5} M (up) and their naked-eye fluorescence change under hand held UV lamp (down).

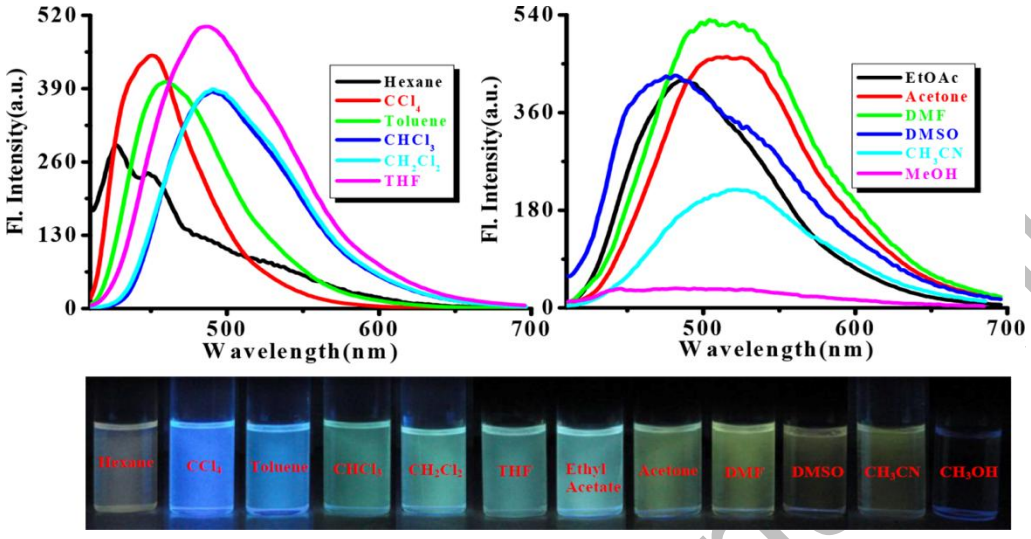


Figure 4. Comparative fluorescence spectra of compound **2d** in different solvents at 1x 10^{-5} M (up) and their naked-eye fluorescence change under hand held UV lamp (down).

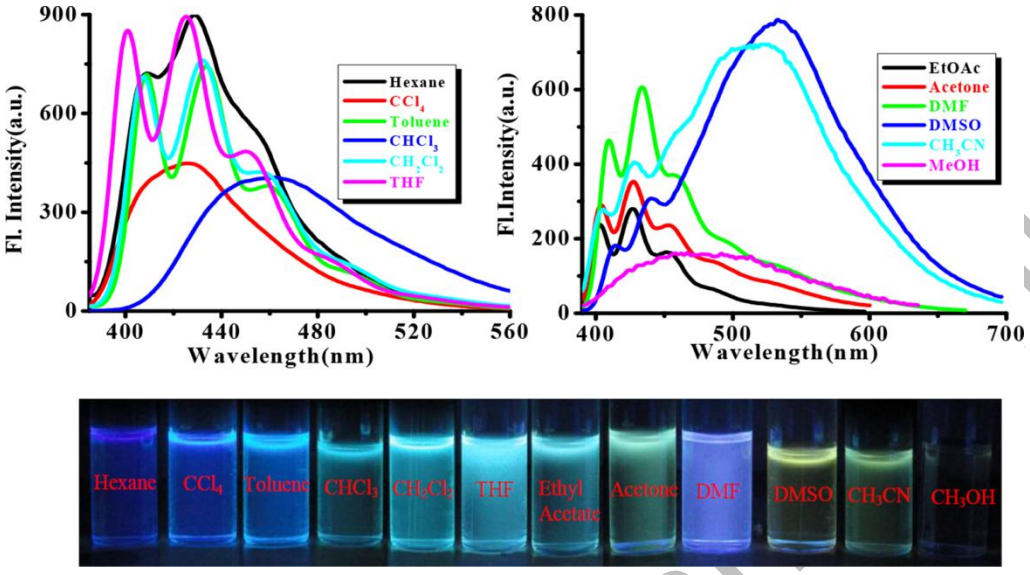


Figure 5. Naked–eye fluorescence change of **1i** (7- Methyl pterin) with different solvents.